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PLAGUE-INFECTED RATS WITHOUT VISIBLE LESIONS.

The Discovery of Bubonic Plague Only in Rats Without Lesions or With Obscure or Apparently Trivial Lesions, After Subsidence of Two Recent Epizootics.

By C. L. WILLIAMS, Surgeon, and T. W. KEMMERER, Bacteriologist, United States Public Health Service.

SUGGESTIVE OBSERVATIONS.

One of the writers of this paper has already emphasized the importance of the occurrence of plague in rats without the appearance of the distinctive lesions of the disease and, in fact, often without any apparent lesions or signs whatsoever. That such cases occasionally were found was mentioned by McCoy (1) and they were later shown by Williams (2) to be of more frequent occurrence than was generally believed. Quite recently there developed in Galveston, Tex., a noteworthy condition which has again brought attention to this subject. Briefly, the condition is this: At intervals over a period of 17 months nine plague-infected rats were found none of which showed physical signs of plague. (*B. pestis* was found in smears in the case of one of these rats.) During the entire 17 months there was not discovered one plague-infected rat which showed visible evidence of infection.

An experienced plague worker will appreciate at once what this means; namely, that without testing, by guinea-pig inoculation, every rat brought into the laboratory, there is the possibility of the belief continuing for months that the infection has disappeared, whereas, in reality, it may be brought into the laboratory in an unrecognized form.

DEVELOPMENT OF PRESENT TECHNIQUE.

For several years the Public Health Service has been bending its effort to perfect the technique of the plague laboratory. The Indian Plague Commission (3), in 1907, definitely established the examination of gross lesions as the most practicable method of diagnosis, and for several years thereafter reliance was placed in this procedure (1)(2), supplemented by guinea-pig inoculations for confirmation. Gradually, however, the belief grew that this alone was not sufficient

for the purpose of an eradicative campaign where the accurate delineation of the infected areas and the reliable determination of absence of infection were matters of importance.

Various ways and means were suggested and tried out. Creel,[1] on several occasions in 1915, ordered the laboratory to make combination inoculations of rats from suspicious localities after they had been reported negative on gross lesions. On three such occasions the inoculated guinea pigs developed plague. This method, however, was not put into general use, the records for the campaign of 1914–1917 showing only 15 such inoculations.[2] Creel also ordered the examination of smears from all rats, and this procedure carried out during the last 18 months of the campaign resulted in the discovery of 17 plague-infected rats that had been passed as negative on inspection of gross lesions (4).[3]

Chapin (5), in 1909, made use of combination inoculations of all rats from a certain suspected locality in Seattle, and Lloyd (6), in 1914, also in Seattle, reports making combination inoculations of all rats in each day's catch (except the few individually inoculated). Probably had these workers discovered infected rats by this method, the procedure would have attracted the attention which it deserved. Doubtless, other workers in this field have used similar methods.

The second outbreak of plague in New Orleans, October, 1919, gave an opportunity for reopening the study of laboratory methods, and the appearance of plague in 1920 in three other Gulf ports rendered it still more important that laboratory technique be perfected. After trying various procedures it finally became evident that mass inoculation of all rats was the method offering the least chance of missing infected rats. This procedure was instituted in New Orleans and later extended to Beaumont and Galveston.

In New Orleans and Beaumont, on account of the large daily catch, it was not possible to inoculate all rats; therefore, the following technique was used: All rats were first examined macroscopically, during which examination they were separated into four groups—positive, suspicious, doubtful, and negative. Those in the suspicious group were individually inoculated on guinea pigs; the negative group was passed on for examination, microscopically, of smears. Smears from as many rats as the force could accommodate (about 200) were examined microscopically, and any rat found suspicious was put, according to degree of suspicion, with the ones separated as "suspicious" or "doubtful" on inspection for gross lesions. The

[1] Surg. R. H. Creel, United States Public Health Service, in charge of plague eradication in New Orleans, La., 1914–1916.

[2] This statement is made from the records of the plague laboratory in New Orleans, La., and has not heretofore been published.

[3] Only 12 of these infected rats are reported in the publication referred to; the other 5 were discovered subsequently.

doubtful group, numbering as a rule, from 30 to 50 rats, was divided into lots of 10, and each lot inoculated in combination on a separate guinea pig.

The doubtful group always consisted only of those rats regarded as possibly infected, but not sufficiently suspicious to warrant individual inoculation. Even during the prevalence of a relatively high infection rate less than one in 500 of the doubtful rats proved infected.

In Galveston, where the catch (after the first few months) was much smaller, the entire catch each day was separated into lots of 10, and each lot was inoculated in combination.

The process of inoculation was to collect a bit of liver and spleen from each rat, place these bits in a small mortar, grind to a paste, add salt solution, mix into an emulsion, and inject 1 c. c. of the emulsion subcutaneously.

The figures given herein are taken from the New Orleans and Galveston records. Combination inoculations did not produce any noteworthy results in Beaumont.

In all probability infected rats showing obscure or no lesions occur during the height of the epizootic as well as at the end—in fact, this has been clearly demonstrated (1) (2)—but we do not pay nearly so much attention to them at that time. The notable thing about the situation is that on the subsidence of the epizootic in New Orleans and Galveston, only cases with obscure or no physical signs were found. This is not at all in agreement with experimental work; for here we find that when rats are inoculated with plague, among those which can later be demonstrated to contain virulent plague bacilli in their tissues, 90 per cent show signs of the disease and not over 10 per cent are without signs.[4]

NEW ORLEANS RATS WITH OBSCURE PLAGUE LESIONS.

In the first New Orleans epizootic (1914–1917), the search for rats with poorly marked plague lesions had not fully developed; however, we find that examination of smears was instituted and, in the last 18 months of the campaign, of 89 infected rats, 17, or 19.1 per cent, were discovered through smear examination only. During the same period, 19 of the 89 rats were diagnosed as resolving plague cases. This is 21.3 per cent. This high proportion of resolving cases is in support of the theory that comparatively few acute cases are trapped, since, in experimental work,[4] the proportion of resolving cases that can be demonstrated by inoculation to retain virulent plague bacilli in their tissues is only about 1 per cent of all demonstrably infected

[4] Results of experimental work here referred to have not yet been published.

rats. Only 7 of these infected rats were discovered during the last six months of this campaign. Of these, 3 were discovered through examination of smears and 2 were resolving cases. The last infected rat was, strangely enough, a well-marked acute case.

For the second New Orleans campaign (1919–1922), better figures are available; but they can not be considered exact for the reason that poorly marked cases were given much less attention in the first year than subsequently. There were found in the laboratory, during the first year, a total of 584 plague-infected rats, of which 68 or 11.6 per cent showed slight or no signs of plague. During this time 89 resolving cases were discovered, or 15.3 per cent of the 584 cases. During the next 10 months, until the time of the last recorded infected rat (August 10, 1921), there were 40 infected rats, of which 14, or 35 per cent, showed poorly marked lesions or were unmarked. Only 3 of the 40 were resolving cases. Only 5 of these 40 rats were found during the last six months of this period. One was a well-marked case, but the last 4 were all rats with obscure or slight signs.

GALVESTON RATS WITH NO PLAGUE LESIONS.

Trapping operations were begun June 20, 1920. The following is a summary of the plague-infected rats found by the usual method of examination for macroscopic lesions and inoculation of guinea pigs from all rats showing lesions suggestive of plague: June, 1920, 8 plague-infected rats; July, 34; August, 10; September, 5; October, 4. None was then found until November 24, when 1 was found. The premises from which this rat was obtained were fumigated and trapping was intensively carried on. Five other infected rats were found December 20, 1920. After this, over a period of 17 months, during which time infected rats were found, none found showed macroscopic lesions of plague. In all, up to December 20, 1920, 66 plague rats were found, of which 2, or 3 per cent showed no visible signs of plague.

After February 8, 1921, in addition to the above method of examination, smears from all rats received at the laboratory were examined microscopically, and, in addition, all of the rats were included in combined inoculation. At first, 10 to 20 rats were included in each lot for mass inoculation, but later the number was limited to 10 or less. As far as it was practicable to arrange it, the rats included in each lot were from the same locality. It might be added that after July 19, 1921, the rats were examined on the same day that they were delivered to the laboratory. Previous to this date the rats were brought in late in the afternoon, put into the ice box, and examined the next morning. This is probably of importance, as putrefaction continues to progress in the ice box, and the guinea

pigs tend to die earlier when putrid material is used for the subcutaneous inoculation.

From February 8, 1921, to the end of May, 1922, more than 19,000 rats were examined in this way, and more than 1,500 combined inoculations were made. One plague rat was found by microscopic examination of smears May 3, 1921. After that date 8 plague-infected rats were found by use of combination inoculations of the total catch. The dates on which these were found are as follows: August 21, 1921; September 21; November 1; December 5; December 12; December 28; January 10, 1922; May 29. During this period not one infected rat showing the gross lesions of plague was discovered.

EVIDENCE OF LOW VIRULENCE.

Toward the end of the 1914 campaign, it was noted by Laughlin (7), and during the present campaign by Williams (both in New Orleans), that when infected rats became very few in number, the test guinea pigs often showed obscure signs, so that three, four, or more pigs would have to be inoculated in succession before sufficiently well-marked signs were secured.

This observation is further borne out by observations in Galveston, where it was noted that the plague organisms in the late cases were apparently of low virulence, as shown by the development of lesions in successive guinea-pig inoculations. In but two inoculations of the last eight infected rats were the lesions of plague well defined in the first guinea pig. In the other six cases the lesions were either absent in guinea pigs dying early, or poorly defined, in those living longer.[5] They did not appear in typical form until the third or fourth consecutive inoculation.

It is interesting here to present some of the concrete evidence of the initial low virulence of the plague bacilli found in some cases. In this respect the last four infected rats discovered in New Orleans were evenly divided. In two instances the first guinea pig inoculated exhibited well-marked evidence of acute plague infection; in the other two instances several inoculations in succession were necessary to establish a diagnosis. The protocols in these four instances are presented below:

Plague rat 972.—Combination inoculation of 11 rats April 13, 1921, subcutaneously. The first guinea pig died in 5 days with obvious acute plague. Two guinea pigs were inoculated cutaneously from the first; both died, in 6 and 7 days, respectively, of acute plague.

Plague rat 973.—Combination inoculation of 11 rats April 30, 1921, subcutaneously. The first guinea pig died in two days of mixed infection, widespread, subcutaneous, hemorrhagic necrosis being the most prominent lesion. Smears from liver and spleen

[5] A routine laboratory rule is to reinoculate from all guinea pigs dying within two days, whether they show signs of infection or not.

showed some suspicious organisms. The second guinea pig inoculated cutaneously from liver and spleen of the first died in six days. At autopsy a few granules on the liver constituted the only gross sign raising suspicion of plague. Smears again showed suspicious organisms. The third guinea pig, inoculated cutaneously from the liver and spleen of the second, died in six days with all the characteristic signs of plague. Two guinea pigs were inoculated cutaneously from liver and spleen; one of these died in three days without any pathological lesion whatever. Smears were negative. The other died in six days and showed at autopsy a small bubo and large spleen with few granules as the only definite plague lesions. Smears showed a few *B. pestis*.

Summary of rat 973.—The first guinea pig died of mixed infection; suspicious smears only pointed to presence of plague. The second guinea pig suggested plague only by few granules on liver and suspicious smears. The third guinea pig was typical acute plague. The fourth lot, two guinea pigs, showed a retrogression of lesions, one dying without signs, the other with poorly developed signs.

Plague rat 974.—Combination inoculation of 12 rats on May 7, 1921, subcutaneously. The first guinea pig died in one day, showing at autopsy gelatinous edema at the site of inoculation. The second, inoculated subcutaneously from material taken from site of inoculation of the first, died in seven days with all the signs of acute plague. Two guinea pigs, inoculated cutaneously from liver and spleen of the second, died in five and six days, respectively, with characteristic signs of acute plague.

Plague rat 975.—Combination inoculation of 10 rats on August 10, 1921, subcutaneously. The first guinea pig died in seven days with a somewhat enlarged and congested liver and spleen. Smears showed a very few suspicious bacilli; these were the only real basis of further inoculations. The second, inoculated cutaneously from liver and spleen of the first, died in ten days, showing at autopsy a right inguinal, partly caseous bubo, small abscesses in the spleen, and a caseous area in one lung. Smears showed a few typical *B. pestis*. It was diagnosed on the table as subacute plague. Four guinea pigs, all inoculated subcutaneously from the liver and spleen of the second, died in four, four, five, and five days, respectively, showing at autopsy the characteristic signs of acute plague. Four guinea pigs were inoculated as follows from one of them: Two were inoculated cutaneously; they lived 12 and 13 days, respectively, the former being killed on the twelfth day, the latter dying on the thirteenth day. The one killed showed at autopsy hard buboes with necrotic centers in both inguinal regions, several large granules in the spleen, and an abscess in the liver. Smears from the spleen showed a few typical *B. pestis*. This animal had shown symptoms of acute illness for several days after inoculation, but had apparently recovered. It is believed that the lesions found were in process of resolution. The animal dying showed at autopsy left inguinal and left pelvic buboes and a nongranular spleen embedded in a large mass of acutely inflamed, partly caseous tissue. It is thought this was a case of subacute or resolving plague with a late acute extension of infection to the tissues surrounding the spleen. The third, inoculated intraperitoneally, died in two days and showed at autopsy acute peritonitis. A smear from the exudate showed apparently a pure culture of *B. pestis*. The fourth, inoculated subcutaneously, died in seven days with characteristic signs of acute plague.

Summary of rat 975.— The first guinea pig showed no lesions ascribed to plague, but it was tested further because of suspicious organisms in smears. The second guinea pig (cutaneously inoculated) lived 10 days and showed signs diagnosed as those of subacute plague. The third lot (subcutaneous inoculation), consisting of four guinea pigs, all showed signs of acute plague. The fourth lot, four guinea pigs, developed mild or subacute plague, acute plague or very severe infection, according as the inoculation was cutaneous, subcutaneous, or intraperitoneal. An interesting observation made on this series was that only one of the ten guinea pigs showed a typical plague liver and spleen, while in five there were no signs of spleen granules whatever.

The inoculation records of the last eight plague-infected rats at Galveston, discovered through mass inoculation methods, are no less interesting. Of these, only two can be said to have caused characteristic acute plague in the first animal inoculated (when the first guinea pig dies in one day, it is judged to have died from causes other than plague infection). The protocols, in brief, follow:

Plague-infected rat No. 69 (mass inoculation No. 534).—The first guinea pig inoculated subcutaneously died in one day with subcutaneous injection and edema as only lesion. The second, inoculated cutaneously from the first, died in seven days with characteristic signs of acute plague, but negative smears. The third, inoculated cutaneously from the second, died in ten days showing usual signs of acute plague.

Plague-infected rat No. 70 (mass inoculation No. 684).—The first guinea pig inoculated subcutaneously died in two days, showing subcutaneous injection and edema as the only lesion; smears negative. The second, inoculated cutaneously from the first, died in 15 days, showing a hemorrhagic lymph node as the only suggestion of a bubo and a suspiciously granular spleen; no other lesions; smears positive. The third, inoculated cutaneously from the second, died in six days with the usual signs of acute plague.

Plague-infected rat No. 71 (mass inoculation No. 772).—The first guinea pig, inoculated subcutaneously, died in two days without lesions of plague. The second, inoculated cutaneously from the first, died in nine days showing caseous buboes and congested spleen with one granule. Smears negative. Diagnosis subacute plague (possibly resolving; guinea pig may have died from some other cause). The third, inoculated cutaneously from second, died in eight days showing caseous bubo as only lesion. Smears negative. The fourth, inoculated cutaneously from the third, died in six days showing as lesions, caseous bubo and granular, though small, spleen. Smears positive. The fifth, inoculated cutaneously from the fourth, died in seven days with typical lesions of acute plague. Smears positive. The sixth, inoculated cutaneously from the fifth, died in five days with usual lesions of acute plague.

Plague-infected rat No. 72 (mass inoculation No. 909).—The first guinea pig, inoculated subcutaneously, died in one day without lesions of plague. The second, inoculated cutaneously from the first, died in 15 days, showing caseous bubo as only lesion. Smears negative. Diagnosis, subacute (possibly resolving) plague. The third, inoculated cutaneously from the second, died in seven days, showing usual lesions of acute plague.

Plague-infected rat No. 73 (mass inoculation No. 933).—The first guinea pig, inoculated subcutaneously, died in two days without lesions of plague. The second, inoculated cutaneously from the first, died in twelve days, showing a caseous bubo and granular spleen. Smears positive. A culture of *B. pestis* was isolated from this guinea pig and further animal-to-animal inoculations were not carried out.

Plague-infected rat No. 74 (mass inoculation No. 988).—The first guinea pig, inoculated subcutaneously, was killed on the ninth day. The lesions were caseous mass at site of inoculation; enlarged, soft, inguinal lymph nodes; slightly enlarged, finely granular spleen. Smears positive. Diagnosis, subacute plague. The second guinea pig, inoculated subcutaneously from the first, died in seven days with usual signs of acute plague.

Plague-infected rat No. 75 (mass inoculation No. 1034).—The first guinea pig, inoculated subcutaneously, died in ten days showing purulent foci in liver as only lesion. Smears negative. The second, inoculated cutaneously from the first, died in six days, showing enlarged inguinal lymph nodes, with beginning caseation at center, and infarct-like area of the liver as the only lesions. Smears negative. The third, inocu-

lated cutaneously from the second, died in four days, showing enlarged congested inguinal lymph nodes and enlarged congested spleen, with appearance suggestive of granules as only lesions. Smears positive. The fourth, inoculated subcutaneously from the third, died in four days, showing typical lesions of acute plague.

Plague-infected rat No. 76 (mass inoculation No. 1649).—The first guinea pig, inoculated subcutaneously, died in three days without lesions of plague. The second guinea pig, inoculated cutaneously from first, was killed on the seventh day. Lesions were suggestive of plague. The third, inoculated cutaneously from the second, died in five days with usual signs of acute plague.

In this series, the confirmation of the diagnosis of plague was by the isolation of the organism in pure culture, which killed white rats and guinea pigs and which was again isolated in pure culture and which showed the microscopic and cultural characteristics of *B. pestis*.

CONCLUSIONS.

The essential points brought out in this paper are that in New Orleans the last four plague rats, discovered between May 4 and August 10, 1921, showed very slight evidence of infection and were discovered only by mass or combination inoculation of considerable numbers of rats, and that in Galveston the last nine plague rats, discovered during the period December 20, 1920, to May 28, 1922, showed no signs of plague (except positive smears in one case, May 3, 1921) and were discovered only by gross or combination inoculations of all rats in each day's catch. The important conclusions are as follows:

1. In making examination of rats to determine the presence of plague, it should be borne in mind that there may be present infected rats showing only obscure or no signs of infection.

2. Such rats with obscure or no signs of plague may be the only plague rats discovered over extended periods of time.

3. To find such rats necessitates, as essential laboratory technique, the inoculation (preferably in groups from various sections of the city) of the entire catch.

4. There is a suggestion arising from observation of the lesions in the inoculated guinea pig that the failure to produce lesions may be a characteristic of the strain of plague bacilli present after subsidence of the acute epizootic.

At present the number of rats in each inoculation is limited to 10, in order not to greatly dilute the collection of organisms that may be present. It remains for future experiments to determine if this number may be safely increased.

COMMENT.

The writers have refrained from drawing any conclusions not fully justified by the data. Obviously the occurrence of infection only in rats with obscure signs or without signs, over considerable periods of time after subsidence of the epizootic, suggests interesting and important possibilities or even probabilities. Certainly these facts support, though they do not prove, a theory that plague infection may exist among rats in an enzootic status with a relationship between the rat and the infecting organism entirely different from that seen during the epizootic period. The observations suggesting lowered virulence of the infecting agent would indicate this to be the principal factor.

It is a very interesting coincidence that while this paper was in process of preparation there should be published by Bordas, Dubieff, and Tannon, (8), working in Paris, an article describing the discovery in Paris of plague-infected rats showing little or no signs of such infection. They state that "* * * when * * * we examine systematically all rats from a locality previously visited by plague, there is always found a certain number of them carriers of Yersin's bacillus which appear in no way diseased." They state that in their opinion the enzootic follows the epizootic and is continued among rats by a strain of *B. pestis* probably attenuated. They also noted that inoculated test animals died slowly and were likely to show few signs of infection. Their data cover more angles of the problem than have been presented herein, together with a discussion of the subject, to the original of which the reader is referred. As mutually confirming each other the observations of those writers and the observations made by us assume added importance.

REFERENCES.

(1) McCoy, G. W.: Plague infection in rats. Article in Public Health Bulletin No. 30, United States Public Health Service.

(2) Williams, C. L.: Diagnosis and detection of rodent plague. Am. Jour. of Pub. Health, November 1920, Vol. 10.

(3) Indian Plague Commission. Jour. of Hygiene, 1907, Vol. VII No. 3.

(4) Williams, C. L.: Diagnosis of plague in rats: The advisability of making routine microscopic examinations of rats, supplementary to the macroscopic examination. Public Health Reports, U. S. Public Health Service, Vol. 31, No. 33, August 18, 1916, p. 2195.

(5) Chapin, C. W.: Report of plague laboratory work. Public Health Reports, Vol. 24, part 1, page 854.

(6) Lloyd, B. J.: In the Annual Report of the Surgeon General of the Public Health Service, 1914, page 243.

(7) Laughlin, J. B.: In the Annual Report of the Surgeon General of the Public Health Service, 1917, page 206.

(8) Bordas, Dubieff, and Tannon: Quelques Considerations sur la Peste et sur les Rats. Presse Médicale, Paris, September 27, 1922, No. 77, page 831.

ON THE MECHANISM OF THE ACTION OF ARSENIC UPON PROTOPLASM.

By CARL VOEGTLIN, Professor of Pharmacology; HELEN A. DYER, Assistant Pharmacologist; and C. S. LEONARD, Associate Pharmacologist, Division of Pharmacology, Hygienic Laboratory, United States Public Health Service.

Introduction.

One of the most hopeful means of extending knowledge of the treatment of disease by drugs is through chemotherapeutic investigations. A phase of these investigations is pharmacodynamic research, which aims at the elucidation of the changes, chemical and physical, produced by chemical substances in the biological unit; namely, the cell. It is in this direction that pharmacology can contribute fundamental information to biology.

The investigator who has the temerity to attack such problems is naturally confronted by great difficulties on account of the complexity of the heterogeneous system which constitutes protoplasm, and for this reason very little or no information is available concerning the cellular action of most chemicals. Textbooks of pharmacology therefore are largely concerned with a description of what might be called the gross or more obvious effects produced by drugs and poisons. This is true of the action of arsenic.

Sollmann, in his Manual of Pharmacology, gives the following summary of the protoplasmic action of this drug: "Schulz (1884) and Binz (1897) attempted to explain the arsenic effects as alternating oxidation and reduction of the cells, due to the easy passage of arsenious and arsenic compounds into each other (which Schulz, 1892, demonstrated on organ emulsions). Husemann, 1892, pointed out that if this were true, both forms should have the same toxicity. The difference is not great for mammals, but very considerable for lower animals and plants (O. Loew). The explanation is therefore not tenable. It is now generally believed that arsenicals hinder oxidation in some unknown way, although Schaefer and Boehm, 1872, showed that arsenic has little effect on ordinary ferments."

In Cushny's book the only reference to the subject is as follows: "No account of the pharmacology of arsenic would be complete without mention of the theory advanced by Binz and Schulz to explain its action. They suppose that arsenious acid is oxidized to arsenic acid by the living tissues, and the arsenic acid again reduced to arsenious. In this way, oxygen is alternately withdrawn from and supplied to the protoplasm, and this alternate reduction and oxidation they suppose to be the essential feature of the action of arsenic. * * * It may suffice here to state that while arsenic acid appears to be reduced and arsenious acid oxidized in the tissues, these processes are probably only gradual. Otherwise it would be difficult to explain how arsenious acid is so much more poisonous

than arsenic acid; for if the latter were readily reduced to arsenious acid, it would be equally toxic."

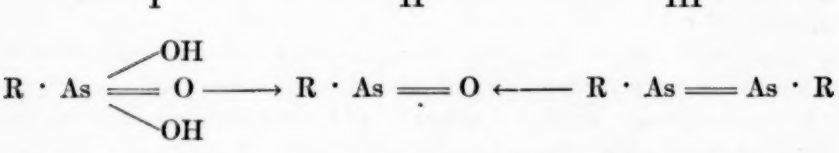
Again, Meyer and Gottlieb state: "Weder die Arsenige noch die Arsensäure gehen ohne weiters mit Bestandteilen des Protoplasmas *erkennbare* oder sonstwie nachweisbare Verbindungen ein: ihre Lösungen sind daher *zunächst* ganz ohne sichtliche morphologische oder funktionelle Wirkung sowohl auf nervöse als auch auf andere organische Gebilde. Nach einiger Zeit aber erlischt das Leben der stark vergifteten Zelle und sie verfällt der postmortalen Zersetzung. Ob diese Wirkung auf katalytischer Hemmung lebenswichtiger Prozesse beruht oder auf chemischer Bindung irgend eines für das Zelleben notwendigen Minimalstoffes des Protoplasmas durch das Arsen, ist nicht bekannt. Fermente werden durch Arsenic nicht merklich beeinflusst, was nicht gerade auf eine 'katalytische' Wirtkung spricht. Für die Möglichkeit einer *specifischen chemischen* Bindung von As spricht dagegen die Angabe von Bertrand (1903), dass As sich als integrierender Bestandteil in allen lebenden Zellen findet."

These quotations from the latest editions of standard books on pharmacology represent the essential information with regard to the protoplasmic action of arsenic, and a thorough review of the original literature scarcely adds anything of moment. Ehrlich (1909) has used his side chain theory to explain the chemotherapeutic action of arsenic. He assumes that trivalent arsenic is firmly fixed to the cell by a definite chemical group (side chain) of protoplasm, this chemical union causing the death of the cell. The only proof offered for this assumption is his observation on arsenic resistant trypanosome strains. Infected mice were repeatedly treated with subcurative doses of atoxyl, until maximum tolerated doses of this drug were no longer capable of clearing the blood of parasites, when it was found that arsacetin was still effective in sterilizing the animals; but if treatment was continued with subcurative doses of arsacetin, the strain gradually became resistant also to this drug; yet arsenophenylglycine was still capable of curing animals injected with the strain resistant to arsacetin. These experiments were interpreted as proof of the theory that the arsenic receptor of the trypanosome had gradually lost some of its power of reacting with arsenic. In spite of the highly interesting nature of these observations, it is well to realize that they do not disclose either the chemical nature of the hypothetic arseno-ceptor, nor do they furnish any valid proof for the formation of a *chemical* combination of arsenic with a protoplasmic constituent.

Plan of Present Investigation.

We intend to report in this paper some observations which throw considerable light on the more intimate mechanism of the action of arsenic upon protoplasm and which are not without importance with reference to their bearing upon the more fundamental problem of biological oxidations and reductions.

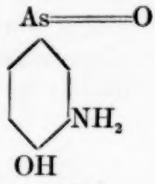
The reasoning which underlies our plan of procedure is briefly as follows: Numerous observations on the relation between chemical constitution and physiological action of a great variety of arsenicals have lead Voegtlin and Smith (1920, 1921) to conclude that arsenic can exert a direct toxic effect only if present in the form R · As═══O, where R represents an aliphatic or aromatic radical. The pentavalent arsenicals and the arsenobenzene derivatives must be converted to this form by means of reduction or partial oxidation, respectively, as expressed by the following formulæ:



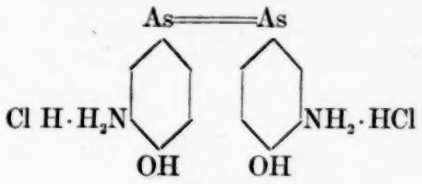
The conversion of the compounds of Groups I and III into compounds of Group II is accomplished by the tissues of the higher animals but not to any appreciable extent by some of the lower forms of life, such as trypanosomes and *Treponema pallidum*. These organisms, however, are highly susceptible to the toxic action of R · As═══O, a fact which can readily be demonstrated by exposing trypanosomes to high dilutions of these arsenicals in the test tube, the organisms being killed within a few minutes, whereas controls exposed to atoxyl or arsphenamine survive exposure to much higher concentrations of these drugs. The same holds true for the parasiticidal effect produced in the infected animal. Minimum effective doses of Groups I and III compounds show a long latent period before destruction of the organisms in the circulating blood begins, whereas injection of R · As ═══ O compounds is followed immediately by a rapid disappearance of the parasites, so that within about 20 minutes the blood is cleared.

The fact that R · As ═══ O compounds are directly toxic explains the great constancy of the results obtained with these compounds in test tube experiments and in the treatment of infected animals, in contrast to the variations observed in work dealing with the pentavalent arsenicals and the arsenobenzene derivatives, which require for the production of the active R · As ═══ O modifications, the intermediate action of the tissues involving a number of variable

factors. For these reasons it was thought best to select for our experiments a representative of the R · As ═══ O compounds, namely, the partial oxidation product of arsphenamine, briefly called "arsenoxide," possessing the constitution—



Arsenoxide.



Arsphenamine.

The questions which have to be answered are: How does "arsenoxide" produce its toxic effect? How does it kill the parasites and what is the mechanism whereby it produces the toxic symptoms in and death of the higher animals? If, according to Ehrlich, the toxic action is primarily due to a chemical reaction between "arsenoxide" and a well-defined chemical group of protoplasm, then it should be possible to overcome the toxic effect of arsenic, at least temporarily, by supplying the parasitic cell or the tissues of animals with an extra amount of the particular protoplasmic constituent containing this reactive group (side chain in Ehrlich's terminology).

Because of the incomplete knowledge regarding the chemical composition of protoplasm generally, it might seem a hopeless task to attempt an attack of the problem in this manner. The situation, however, was made considerably less complex by a proper appreciation of some well-known chemical properties of arsenic. In qualitative and quantitative analyses, use is made of the great reactivity of arsenite with H_2S, as expressed by the equation—

$$2\ As(OH)_3 + 3\ H_2S = 6\ H_2O + As_2S_3$$

Aromatic arsenious oxides (R·As═══O), including arsenoxide, also react with the greatest ease with H_2S according to the equation—

$$R \cdot As{:}O + H_2\,S = R \cdot As{:}S + H_2O$$

A similar reaction takes place when a sulphydryl compound (R·SH) is used instead of H_2S:

$$As\begin{matrix}OH\\OH\\OH\end{matrix} + \begin{matrix}HS\cdot CH_2\cdot COOH\\HS\cdot CH_2\cdot COOH\\HS\cdot CH_2\cdot COOH\end{matrix} = As\begin{matrix}S\cdot CH_2\cdot COOH\\S\cdot CH_2\cdot COOH\\S\cdot CH_2\cdot COOH\end{matrix} + 3H_2O$$

It was therefore quite logical to consider the possibility that arsenic might react with a protoplasmic constituent containing sulphur, especially as Heffter, several years ago, had demonstrated

the fact that tissues contain a substance which, from its behavior against sodium nitroprusside and sulphur, may be considered as a "proteinlike" substance containing a sulphydryl (SH) group. This compound was held responsible for the reducing properties of fresh tissues. It remained for Hopkins (1921) to isolate from yeast and mammalian tissues, glutathione, a dipeptide, containing glutaminic acid and cystein. This remarkable substance is autoxidizable, its sulphydryl group undergoing the following reversible change:

$$\begin{matrix} R\cdot SH \\ R\cdot SH \end{matrix} \rightleftarrows R\cdot S\text{——}S\cdot R$$

Hopkins, and Hopkins and Dixon, by means of experiments on surviving frog's and mammalian muscle, demonstrated that glutathione was concerned in biological oxidations and reductions.

According to Hopkins, fresh ox muscle and brewer's yeast contain about 100 to 150 milligrams of glutathione per kilo, and liver is considered to be somewhat richer in this substance. The fact that the absolute mass of glutathione in tissues, and the amount of arsenoxide necessary to produce a toxic effect are both small, *a priori* speaks in favor of our assumption of a chemical interaction between the two substances.

It was therefore decided to subject to experimental proof the hypothesis that the toxic action of arsenic is due to an effect upon glutathione or some closely related sulphydryl compounds.

Experimental.

For the sake of clearness, the investigation can be divided into two parts: (A) Experiments which deal with the demonstration of the antagonistic action of arsenoxide and certain sulphydryl compounds on trypanosomes, and (B) observations on the antagonism of arsenoxide and sulphydryl compounds in a representative of the higher animals, namely, the albino rat.

The arsenoxide (3–amino–4–hydroxy–1–phenylarsenious oxide) was prepared as the hydrochloride by Dr. J. M. Johnson, of the Hygenic Laboratory. It represents a white, amorphous powder, easily soluble in cold water, and stable if kept in an amber-colored glass bottle in a vacuum desiccator. Analysis of this lot of arsenoxide showed that it was unusually pure.

Glutathione was prepared from yeast or ox liver, following the directions described by Hopkins (1921). The final product was either the oxidized form or the reduced dipeptide. The latter was obtained in the form of a gum by decomposing the copper hydroxide or final mercury precipitate with H_2S and allowing the filtrate from Cu_2S or Hg_2S, respectively, to evaporate in a vacuum desiccator over phosphorus pentoxide. The reduced form, in every

instance, gave an intense nitroprusside test, whereas the oxidized form of the substance (R·S——S·R) did not yield this test.

In order to confirm the results obtained with glutathione prepared in this laboratory, Prof. Gowland Hopkins very kindly supplied us with a small amount of the pure oxidized form of glutathione. A part of this material was converted into the reduced dipeptide by dissolving it in water and adding the mercuric sulphate reagent. The insoluble mercury derivative thus formed was filtered, washed thoroughly with water, suspended in a small amount of water, and treated with H_2S. The filtrate from the mercurous sulphide was evaporated in a vacuum desiccator over P_2O_5, leaving a colorless, gummy mass. The product gave a strong nitroprusside test, indicating the presence of the SH group.

Besides testing the influence of glutathione on the arsenoxide action, it seemed desirable to study also the effect of other sulphydryl compounds and their corresponding disulphide (R·S——S·R) modifications. The following substances were prepared: Cystein hydrochloride and cystine, thioglycollic acid, and dithiodiglycollic acid, α—thiolactic acid, glycyl–cystein, thiosalicylic acid, and dithiodisalicylic acid. The latter two compounds were prepared by Dr. M. X. Sullivan, of the division of chemistry, Hygienic Laboratory.

Glycyl-cystein was prepared by the method of Emil Fischer and U. Suzuki (1904) for diglycylcystine, except that in the last stage the material was precipitated with mercuric sulphate reagent and the mercury compound decomposed with H_2S; the filtrate of Hg_2S, on evaporation in the desiccator, yielded the reduced dipeptide as a thick, yellowish syrup. The microkjeldahl gave 4.495 per cent N; theory for glycyl-cystein, $H_2SO_4 \cdot 2H_2O$=4.487 per cent N.

Cystein hydrochloride was prepared from pure cystine by tin reduction, removal of excess metal with H_2S, and evaporation in vacuum.

In control experiments the following pure amino-acids were used: d–alanine, l–aspartic acid, d–glutaminic acid, l–histidine, l–leucine, l–tryptophane, l–tyrosine, and d–valine.

We are indebted to Doctor Jones, of the Bureau of Chemistry, Department of Agriculture, for the samples of valine and aspartic acid.

A. TRYPANOSOME EXPERIMENTS.

As in previous work, we selected for this investigation our standard strain of *Trypanosoma equiperdum*, which is propagated in albino rats.

In order to obtain simple conditions, the antagonistic action of the sulphydryl compounds was first tested out *in vitro*. For this purpose, a rat showing about 100,000 to 150,000 trypanosomes per c. mm. was bled into 10 c. c. 2 per cent sodium citrate. A series

of small test tubes (80 mm. long and 8 mm. wide) was charged successively with various dilutions of arsenoxide in 0.8 per cent sodium chloride solution and always the same volume of trypanosome suspension. The final concentration of arsenoxide in each tube is always expressed in terms of molecular concentration; i. e., the number of gram-molecules per liter. Small drops of the contents of each tube were removed by glass rods to microscopic slides at various intervals after the exposure of the parasites to the drug and were examined microscopically as to loss of motility of the organisms. Loss of motility is considered as a pretty reliable index of the killing power of a certain concentration of arsenoxide, because it was shown that trypanosomes which had become immotile, when injected into rats, had completely lost their virulence, the animals remaining sterile. Furthermore, loss of motility is soon followed by disintegration of the organisms if kept *in vitro*.

The effect of various concentrations of arsenoxide upon *Tr. equiperdum in vitro* is illustrated in Table I. It is evident that arsenoxide is highly toxic to trypanosomes and, furthermore, that the toxic action is a function of the concentration of the drug, as the time required to cause loss of motility increases with decreasing concentrations. Control tubes containing no arsenoxide always showed actively motile organisms long after the experiment was discontinued.

TABLE I.—*Trypanocidal action of arsenoxide in vitro.*

Arsenoxide.	0.8% NaCl added.	Trypanosome suspension added.	Final arsenoxide concentration.	Time.	Length of life (minutes).	Remarks
c.c.	*c. c.*	*c. c.*				
.....	0.5	0.5	.....	2:40	[1] 115	2:48 very motile. 4:00 very motile. 4:35 very motile.
0.1 M/1,000.....	.4	.5	M/10,000.....	2:47	<6	2:48 some motile. 2:53 immotile.
0.1 M/2,000.....	.4	.5	M/20,000.....	2:52	<15	3:00 some motile, some immotile. 3:07 immotile.
0.1 M/4,000.....	.4	.5	M/40,000.....	2:59	<21	3:10 few sluggish, remainder immotile.
0.1 M/8,000.....	.4	.5	M/80,000.....	3:01	28	3:14 motile. 3:20 some sluggish, remainder motile. 3:29 trace only sluggish.
0.1 M/16,000.....	.4	.5	M/160,000.....	3:02	45	3:14 motile. 3:22 motile. 3:30 motile. 3:47 only few motile.
0.1 M/32,000.....	.4	.5	M/320,000.....	3:05	90	3:30 motile. 3:50 motile. 4:00 motile. 4:15 very few motile. 4:35 immotile.
0.1 M/64,000.....	.4	.5	M/640,000.....	3:07	[2] 88	3:35 motile. 4:17 motile. 4:35 like control.
0.1 M/128,000....	.4	.5	M/1,280,000....	3:11	[2] 84	3:35 motile. 4:17 motile as control. 4:35 like control.
0.1 M/256,000....	.4	.5	M/2,560.000....	3:19	[2] 76	3:35 motile. 4:17 motile as control. 4:35 like control.

[1] Very motile. [2] As motile as control

We call particular attention to the fact that M/20,000 arsenoxide causes complete loss of motility of all organisms in less than 15 minutes. This is about the concentration which obtains in the circulating blood of an infected rat after injection of a dose of arsenoxide which will clear the blood in approximately 15 minutes. There is therefore an excellent agreement between the lethal concentration of this drug established *in vitro* and *in vivo*.

The experiments, which demonstrate the detoxifying effect of certain sulphydryl compounds (including glutathione) on arsenoxide, are described in some detail in Tables II to IV. These data leave no doubt as to the powerful antagonistic effect of these sulphydryl compounds on the toxic action of arsenoxide. For instance, in the presence of M/20 sodium thioglycollate the trypanosomes are still actively motile after exposure for an hour or longer to M/200 arsenoxide, a concentration of the latter drug which is *one hundred* times greater than the one (M/20,000) which will kill the organisms in less than 15 minutes in the absence of thioglycollate. Dithiodiglycollate[1] is much less effective, a point which will be referred to later.

Cystein also exhibits a marked detoxifying effect, and so does glutathione in the reduced form.

Numerous control experiments in which various amino acids containing no sulphur, glucose, or lecithin were used instead of the SH compounds yielded negative results.

TABLE II.—*Antagonistic action of glutathione (reduced) on trypanocidal action of arsenoxide in vitro.*

Concentration of preparation.	Time (minutes).						
	5	10	15	20	30	40	60
Glutathione M/10	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.
Glutathione M/40	Immotile.						
Arsenoxide M/200							
Glutathione M/20	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.
Arsenoxide M/200							
Glutathione M/80	Immotile.						
Arsenoxide M/400							
Glutathione M/40		Motile.		Motile.	Motile.	Sl. sluggish.	Sl. sluggish.
Arsenoxide M/400							
Glutathione M/25	Motile.	do.	Motile.	do.	do.	Motile.	Motile.
Arsenoxide M/400							
Glutathione M/320	Immotile.						
Arsenoxide M/4,000							
Glutathione M/160	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.
Arsenoxide M/4,000							

Incidentally it may be mentioned that very high concentrations of these SH compounds *per se* exert a toxic effect upon trypanosomes,

[1] A solution of dithiodiglycollate contains, of course, twice as much sulphur as an equimolecular solution of thioglycollate.

a fact which is not at all surprising when it is remembered that they contain a very reactive SH group, a sudden excess of which might seriously interfere with the chemical equilibrium on which the life of the trypanosome depends.

These experiments then strongly point to a biological antagonism between arsenoxide and the sulphydryl compounds mentioned above.

It was decided to attempt to confirm these results by exposing trypanosomes in their natural habitat—i. e., the circulating blood of the rat—to the action of these various compounds. If these *in vivo* experiments should confirm the results obtained in the test tube, there could not possibly be any ground for criticism.

The rats used weighed between 100 and 120 grams, and were inoculated with the standard strain of *Tr. equiperdum* the day preceding the experiment. Only such animals were selected as showed between 100,000 and 200,000 parasites per cubic millimeter of blood. The food was withdrawn about 18 hours previous to the test in order to eliminate any possible disturbing influence of digestion and absorption of food. The technique was the same as that employed in our previous work, the drug injections being made into the leg vein. The concentration of the drug solutions was so adjusted that the total amount of fluid injected never exceeded 1 cubic centimeter per rat.

TABLE III.—*Antagonistic action of cystein on trypanocidal action of "arsenoxide" in vitro.*

Concentration of preparations.	Time (minutes).						
	5	10	15	20	30	40	60
Cystein sod. M/20	Sluggish.	Sluggish.		Immotile.			
Cystein sod. M/40	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.	Motile.
Cystein sod. M/40	do.	do.	do.	do.	Sluggish.	Immotile.	
Arsenoxide M/200							
Cystein sod. M/80	do.			Sluggish.		do.	
Arsenoxide M/400							
Cystein sod. M/80	do.	Motile.	Motile.	Motile.	Motile.	Motile.	Do.
Arsenoxide M/800							
Cystein sod. M/160	do.	do.	do.	do.	do.	do.	Do.
Arsenoxide M/3200							

The minimum effective dose of the arsenoxide used was 0.5 c. c. M/100 per kilo body weight of rat. It was shown in a very large number of experiments that injection of this dose is followed without fail by an immediate and progressive reduction of the number of parasites and the blood is regularly cleared in about 30 minutes. In order to make the results more striking, a larger dose—i. e., 0.75 c. c. M/100 per kilo—was used. This dose yields an action curve which, if traced on logarithmic paper, presents a straight line.

As arsenoxide produces its effect upon the parasites in the circulating blood with such great rapidity, it was necessary to precede its

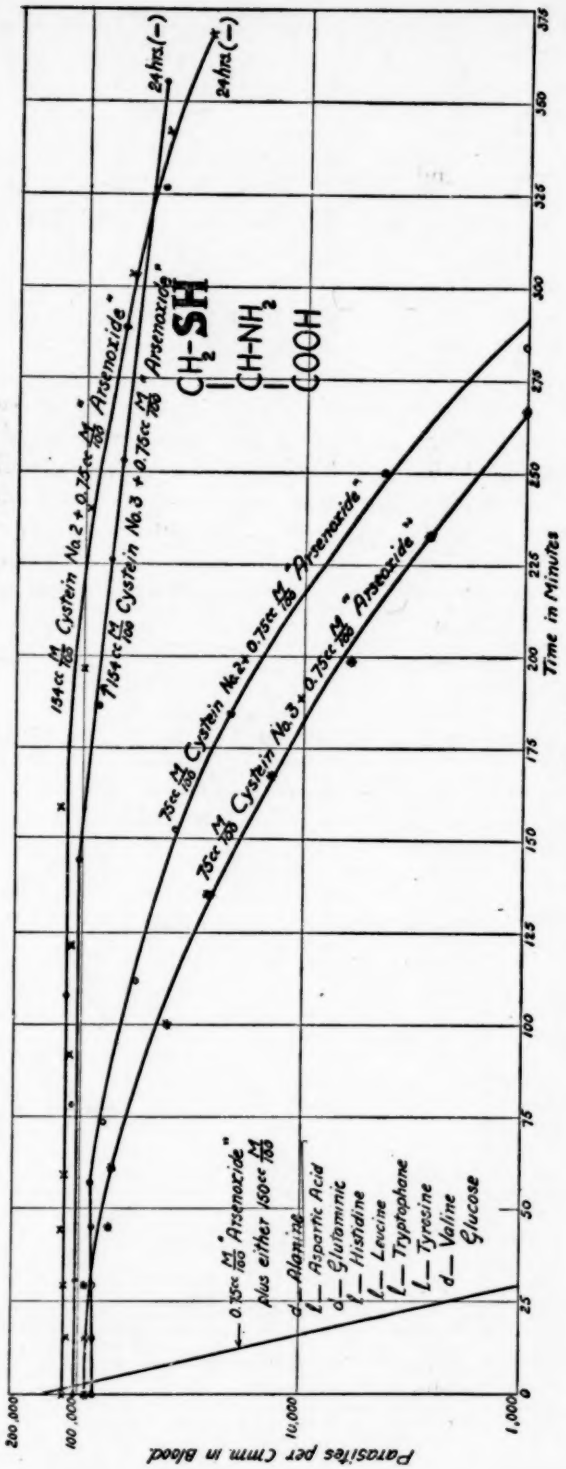

Parasites per Cmm. in Blood
200,000
100,000
10,000
1,000
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
Time in Minutes
24 hrs (−)
24 hrs (−)
1.54 cc M/100 Cystein No. 2 + 0.75 cc M/100 "Arsenoxide"
1.54 cc M/100 Cystein No. 3 + 0.75 cc M/100 "Arsenoxide"
.75 cc M/100 Cystein No. 2 + 0.75 cc M/100 "Arsenoxide"
.75 cc M/100 Cystein No. 3 + 0.75 cc M/100 "Arsenoxide"
CH2-SH
CH-NH2
COOH
0.75 cc M/100 "Arsenoxide" plus either 150 cc M/100
d— Alanine
l— Aspartic Acid
d— Glutamine
l— Histidine
l— Leucine
l— Tryptophane
l— Tyrosine
d— Valine
Glucose

CHART 1.

administration by the injection of the particular antagonist under consideration.[2] The time intervening between the two injections was about one minute, except in certain experiments which will be dealt with later.

The effect of the various sulphur compounds on the action curve of arsenoxide is illustrated by Charts 1 to 5. For instance, Chart 1 shows the remarkable fact that the injection of 154 c. c. M/100 cystein (No. 2) per kilo completely inhibits the trypanocidal action of the subsequent injection of 0.75 c. c. M/100 arsenoxide for more than three hours. Half the amount of cystein (75 c. c. M/100) produces a latent period of the arsenoxide action of 60 minutes, and almost five hours are required to reduce the parasite count to 1,000 per c. mm. The remarkable detoxifying action of cystein is in striking contrast to the absence of any such effect when, instead of cystein, other amino-acids are injected one minute before the arsenoxide. These amino-acids (and also glucose) have no influence whatsoever on the action curve of arsenoxide.

TABLE IV.—*Antagonistic action of sodium thioglycollate and sodium dithiodiglycollate on trypanocidal action of "arsenoxide" in vitro.*

Concentration of preparations.	Time (minutes).						
	5	10	15	20	30	40	60
Control in NaCl	Motile	Motile	Motile	Motile	Motile	Motile	Motile.
Arsenoxide M/20,000	do	Immotile					
Arsenoxide M/80,000	do	Motile	Motile	Sl. motile	Immotile		
Arsenoxide M/320,000	do	do	do	Motile	Motile	Motile	Do.
Thioglycollate neut. M/5	Immotile						
Thioglycollate neut. M/10	Motile	Motile	Motile		Sl. motile		Sluggish.
Thioglycollate M/10 / Arsenoxide M/100			Sluggish	Sluggish		Immotile	
Thioglycollate M/40 / Arsenoxide M/200	Motile	Motile	Motile		Sl. motile		Immotile
Thioglycollate M/20 / Arsenoxide M/200	do	do	do	Motile	Motile		Sluggish.
Thioglycollate M/80 / Arsenoxide M/400	do	do	do	do		Sluggish	Immotile.
Thioglycollate M/40 / Arsenoxide M/400	do	do	do	do	Motile	Motile	Motile.
Thioglycollate M/80 / Arsenoxide M/800	do	do	do	do	do	do	Do.
Thioglycollate M/800 / Arsenoxide M/10,000	Sl. motile	Immotile					
Thioglycollate M/400 / Arsenoxide M/10,000	Immotile	Motile	Motile	Motile	Motile	Motile	Do.
Dithiodiglycollate M/10	Immotile						
Dithiodiglycollate M/20	Motile	Motile	Motile	Motile	Motile	Motile	Motile.
Dithiodiglycollate M/20 / Arsenoxide M/400	do	Immotile					
Dithiodiglycollate M/20 / Arsenoxide M/800	do	Motile	Motile	Motile	Motile	Motile	Do.
Dithiodiglycollate M/320 / Arsenoxide M/10,000		Sl. motile		Immotile			
Dithiodiglycollate M/160 / Arsenoxide M/10,000	Motile	Motile	Motile	Motile	Motile	Motile	Do.

[2] The reaction of the solutions was always adjusted to neutrality.

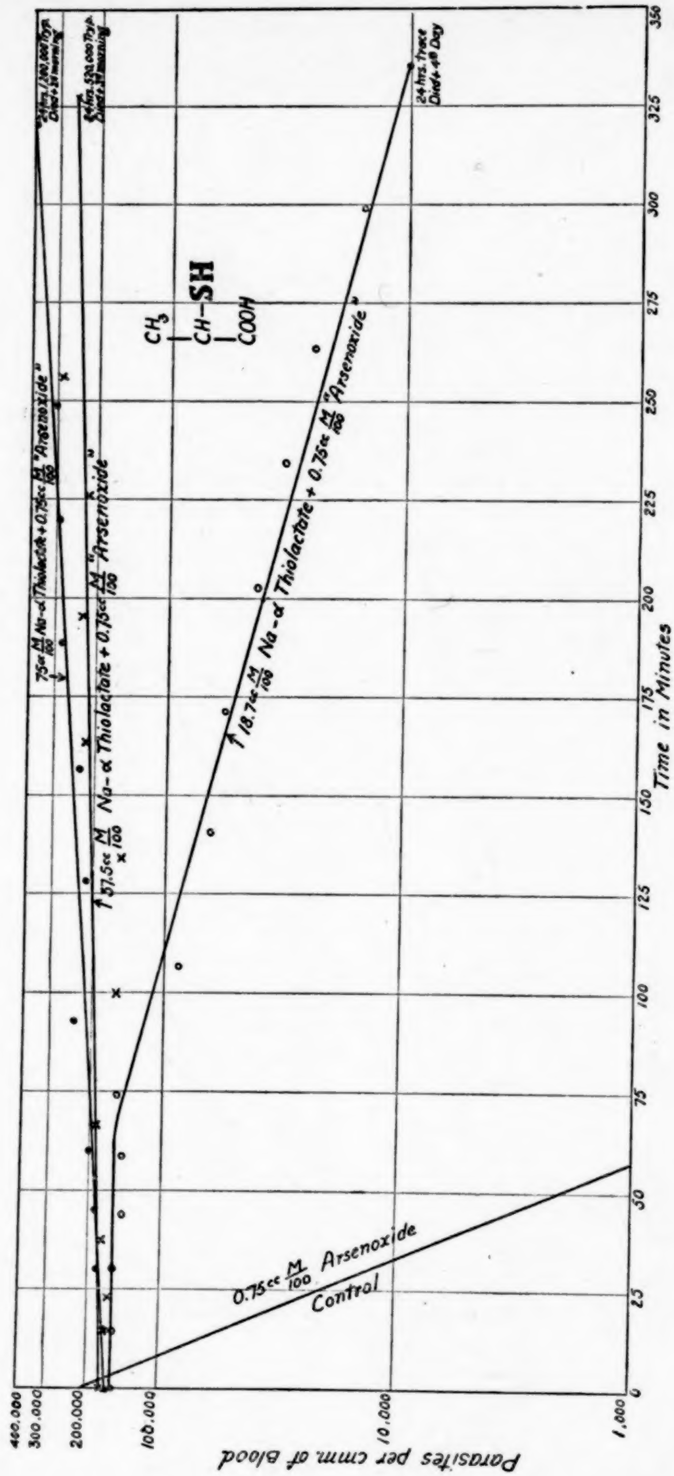

Parasites per cmm. of Blood
Time in Minutes
0.75cc M/100 Arsenoxide
Control
18.7cc M/100 Na-α Thiolactate + 0.75cc M/100 "Arsenoxide"
37.5cc M/x100 Na-α Thiolactate + 0.75cc M/100 "Arsenoxide"
75cc M/100 Na-α Thiolactate + 0.75cc M/100 "Arsenoxide"
24 hrs. Trace Died + 4th Day
CH3
CH-SH
COOH
400,000
300,000
200,000
100,000
10,000
1,000

CHART 2.

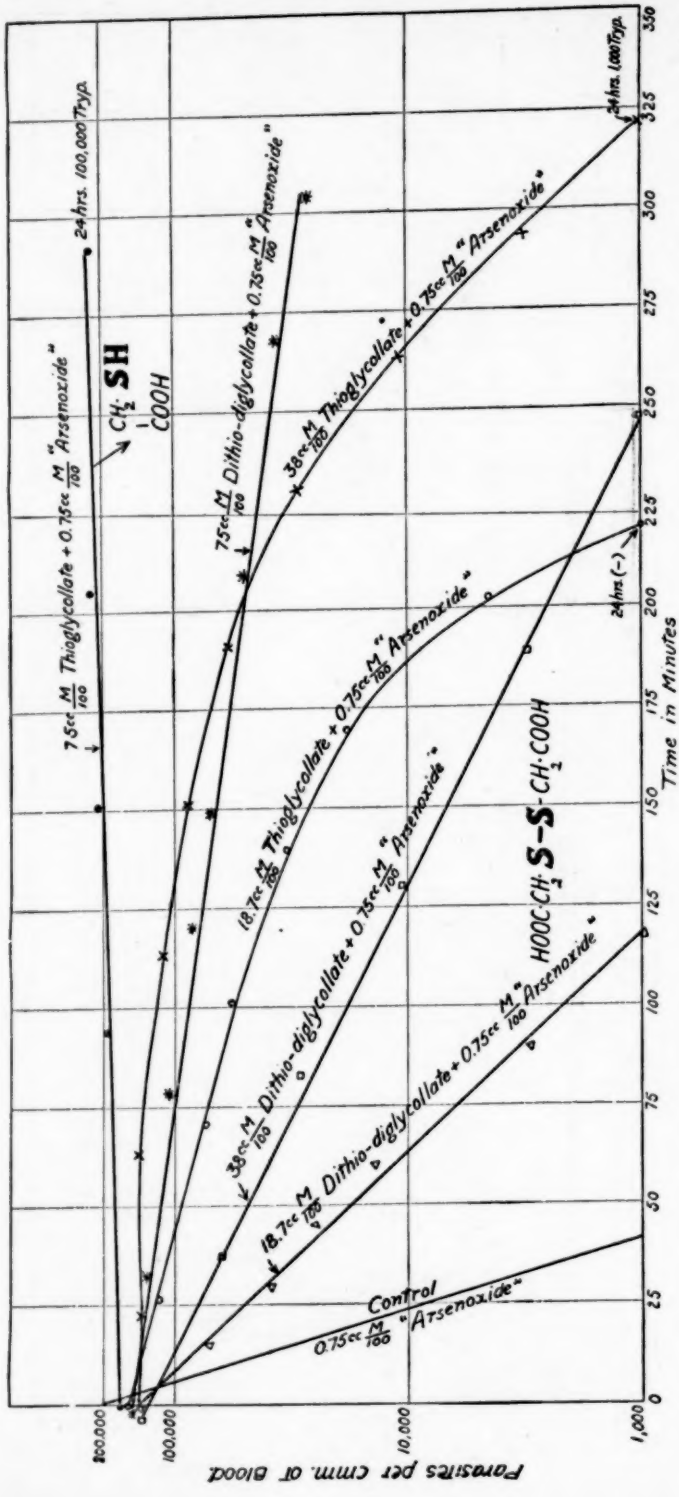

Parasites per cmm. of blood
100,000
10,000
1,000
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
Time in Minutes
24 hrs. 100,000 Typ.
24 hrs. (-)
24 hrs. 1,000 Typ.
7.5cc M/100 Thioglycollate + 0.75cc M/100 "Arsenoxide"
CH2 SH
COOH
7.5cc M/100 Dithio-diglycollate + 0.75cc M/100 "Arsenoxide"
3.8cc M/100 Thioglycollate + 0.75cc M/100 "Arsenoxide"
1.87cc M/100 Thioglycollate + 0.75cc M/100 "Arsenoxide"
3.8cc M/100 Dithio-diglycollate + 0.75cc M/100 "Arsenoxide"
1.87cc M/100 Dithio-diglycollate + 0.75cc M/100 "Arsenoxide"
HOOC·CH2 S-S CH2·COOH
Control
0.75cc M/100 "Arsenoxide"

CHART 3.

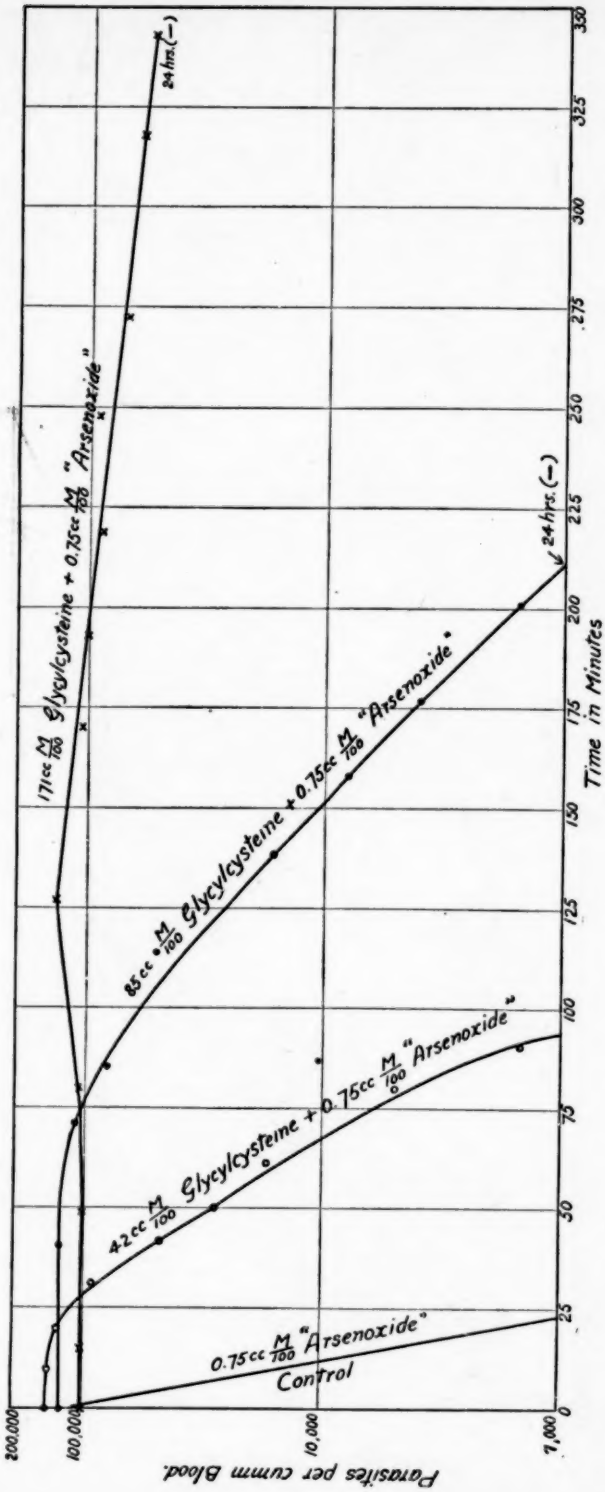

24 hrs.(−)
1.7 cc M/100 Glycylcysteine + 0.75 cc M/100 "Arsenoxide"
24 hrs.(−)
8.5 cc M/100 Glycylcysteine + 0.75 cc M/100 "Arsenoxide"
4.2 cc M/100 Glycylcysteine + 0.75 cc M/100 "Arsenoxide"
0.75 cc M/100 "Arsenoxide"
Control
Parasites per cumm Blood.
200,000
100,000
10,000
1,000
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
Time in Minutes

CHART 4.

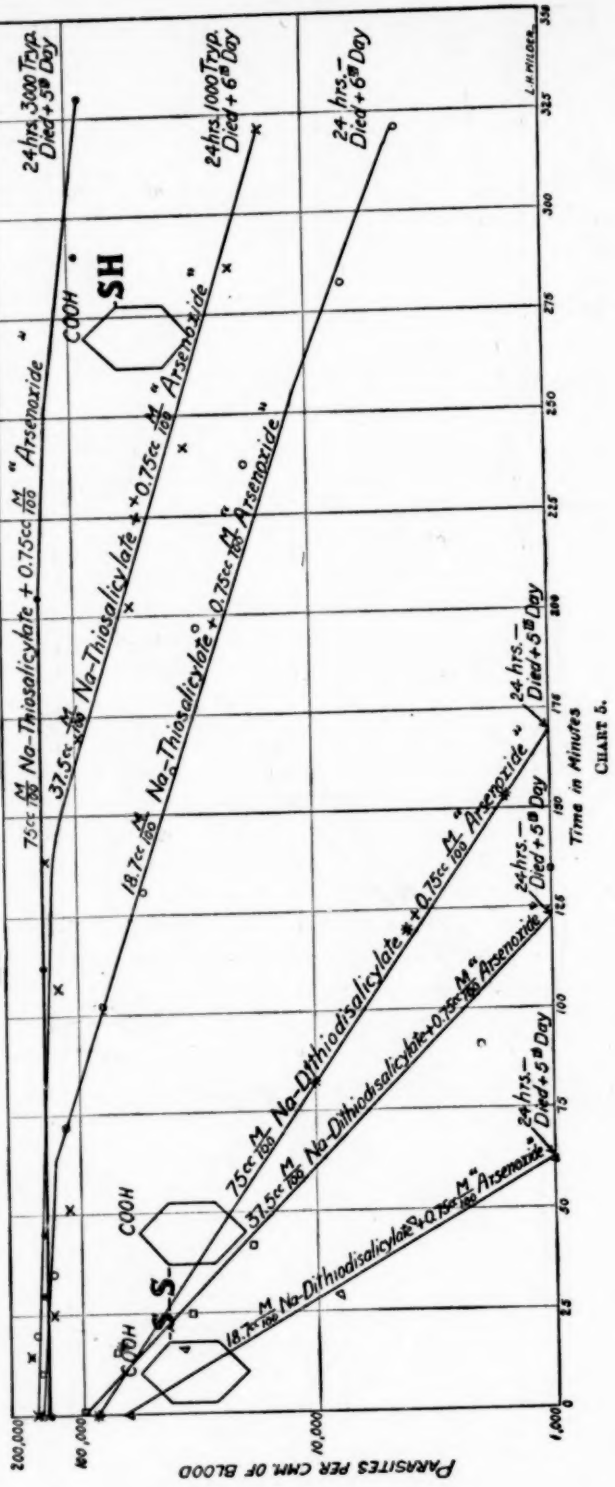

24 hrs. 3000 Tryp. Died + 5th Day
24 hrs. 1000 Tryp. Died + 6th Day
24 hrs. — Died + 6th Day
75cc M/100 Na-Thiosalicylate + 0.75cc M/100 "Arsenoxide"
37.5cc M/100 Na-Thiosalicylate + 0.75cc M/100 "Arsenoxide"
18.7cc M/100 Na-Thiosalicylate + 0.75cc M/100 "Arsenoxide"
COOH
SH
24 hrs. — Died + 5th Day
75cc M/100 Na-Dithiodisalicylate + 0.75cc M/100 "Arsenoxide"
37.5cc M/100 Na-Dithiodisalicylate + 0.75cc M/100 "Arsenoxide"
18.7cc M/100 Na-Dithiodisalicylate + 0.75cc M/100 "Arsenoxide"
S-
Parasites per cmm. of blood
200,000
100,000
10,000
1,000
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
L.H. Hilder
Time in Minutes

CHART 5.

α–Thiolactate (sodium salt) is even more effective than cystein in overcoming the arsenoxide action, as shown by Chart 2. It will be noted that 75 c. c. M/100 permanently prevents the action of a dose of arsenoxide which by itself promptly clears the blood of parasites. The number of trypanosomes, instead of decreasing, increases as if no drug had been injected; and 24 hours after the injection, the blood shows the enormous number of 1,200,000 per cmm., and the animal is found dead of the disease the following morning. The antagonistic effect of α–thiolactate is still complete with a dose of 37.5 c. c., and even 18.7 c. c. delays the arsenic action enormously.

Sodium thioglycollate, glycylcystein, and sodium thiosalicylate also exert a powerful detoxifying action (Charts 3 to 5).

Various lots of reduced glutathione (Chart 6), including the one prepared from the sample supplied by Professor Hopkins, showed essentially the same effect as the other sulphydryl compounds, although somewhat less marked.[3]

The detoxifying effect of sulphydryl compounds is also shown in Table V. It will be noted that the minimum effective dose of arsenoxide, when preceded by 100 c. c. M/100 thioglycollate per kilo, is five times greater than that of arsenoxide alone. (A similar but less marked detoxifying effect is also seen in the case of dithiodiglycollate.)

In view of the autoxidizable properties of the SH group of these compounds it appeared of interest to perform some experiments with the corresponding oxidized modifications (R · S——S · R); 75 c. c. M/100 cystine (as sodium salt) had only a slight retarding effect on the arsenoxide action curve. Dithiodisalicylate was somewhat more effective, and dithiodiglycollate showed quite a marked antagonistic effect, which, however, does not nearly approach that of equivalent molecular amounts of the reduced modification. The oxidized form of glutathione (R · S——S · R), given in doses of 75 c. c. M/100 12 or 45 minutes before arsenoxide, had practically no effect upon the action of the latter compound. The reason for prolonging the interval between the injection of the two substances was to give the parasites and the tissues of the body a chance to convert the oxidized form into the SH modification.

[3] Sodium sulphocyanide gave no protection. This substance does not give a nitroprusside test. Sodium thiosulphate and sulphite, $FeCl_2$ and $FeCl_3$, were without effect.

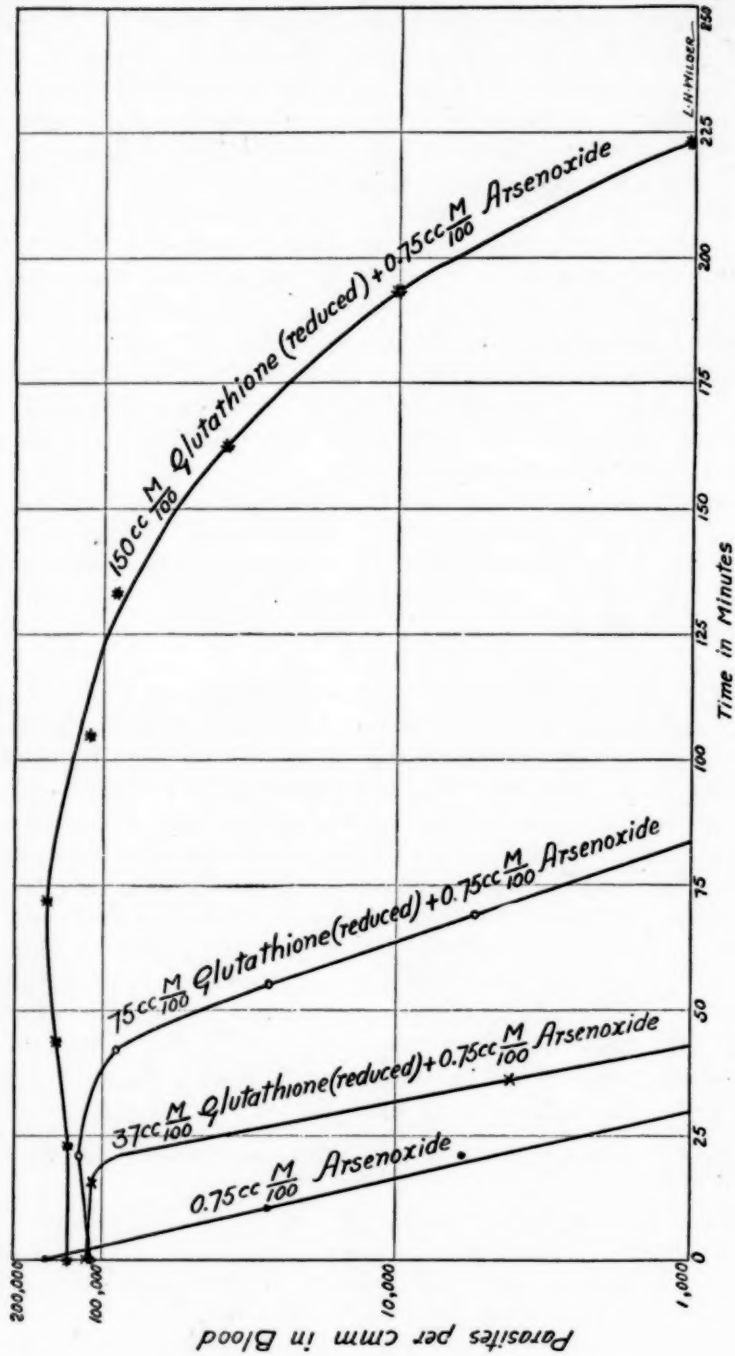

150cc M/100 Glutathione (reduced) + 0.75cc M/100 Arsenoxide
75cc M/100 Glutathione (reduced) + 0.75cc M/100 Arsenoxide
37cc M/100 Glutathione (reduced) + 0.75cc M/100 Arsenoxide
0.75cc M/100 Arsenoxide
Time in Minutes
Parasites per cmm in Blood
200,000
100,000
10,000
1,000
0
25
50
75
100
125
150
175
200
225
250

CHART 6.

TABLE V.—*Effect of sodium thioglycollate and dithiodiglycollate on the minimum effective dose of arsenoxide.*

Dose, c. c. 1/100 As equivalent solution per K.	Arsenoxide alone.			100 c. c. M/100 per kilo thioglycollate followed by arsenoxide.			
	Initial count.	24-hour examination.	48-hour examination.	Initial count.	24-hour examination.	48-hour examination.	72-hour examination.
0.5	80,000	(−)	(−)	132,000	820,000	Dead.	.....
	124,000	(−)	(−)	85,000	+++++	Dead.	.....
	138,000	(−)	(−)	53,000	700,000	+++++D	.....
	120,000	(−)	(−)	.....	.....	.....	.....
	230,000	(−)	(−)	.....	.....	.....	.....
1.0	100,000	(−)	(−)	75,000	248,000	+++++	Dead.
				108,000	464,000	Dead.	.....
1.5	.....	.....	.....	92,000	2,000	+++	++
				100,000	400,000	+++++	Dead.
				104,000	30,000	++++	Dead.
2.0	.....	.....	.....	160,000	2,000	+	++
				130,000	(−)	(−)	(−)
				100,000	(−)	(−)	(−)
				200,000	(−)	(−)	(−)
2.5	.....	.....	.....	190,000	(−)	(−)	(−)
				240,000	(−)	(−)	(−)
				210,000	(−)	(−)	(−)
				100 c. c. M/100 per K dithiodiglycollate followed by arsenoxide.			
0.5	102,000	(−)	+	124,000	360,000	Dead.	.....
	128,000	(−)	(−)	108,000	1,200,000	Dead.	.....
	138,000	(−)	(−)	120,000	1,152,000	Dead.	.....
1.0	.....	.....	.....	110,000	Trace.	(−)	.....
				110,000	(−)	+++	.....
				106,000	Trace.	++	.....
				112,000	(−)	(−)	.....
				130,000	1,000	+	.....
1.5	.....	.....	.....	104,000	(−)	(−)	.....
				108,000	(−)	(−)	.....
				120,000	(−)	(−)	.....
				100,000	(−)	(−)	.....

The fact that the R·S——S·R compounds are, without exception, either much less active or devoid of all inhibiting action indicates that the essential active group is the sulphydryl group, and that the radical to which it is attached is only of secondary importance.

In a further series of experiments an attempt was made to determine *the persistence of the antagonistic action of certain sulphydryl compounds on the trypanocidal action of arsenoxide.* A constant dose of the SH compound was injected intravenously into a series of rats, and this was followed, at various intervals, by an intravenous injection of arsenoxide. The number of parasites in the blood was then

determined over a period of several hours. The injection of the SH compounds alone has no effect on the number of parasites. Chart 7 illustrates the experiments with cystein, when the sodium salt of this substance was injected 1, 12, 30, 60, and 120 minutes, respectively, before the arsenoxide. (The zero point of the curves corresponds to the time when the arsenoxide was injected.) The results are clear-cut and show that the detoxifying effect of cystein is gradually reduced as the interval between the injection of the SH compound and the arsenoxide is lengthened. A similar series of experiments with sodium thioglycollate and arsenoxide is illustrated by Chart 8. Here, also, the detoxifying effect of the SH compound gradually diminishes with the increase in the time interval between the two injections. What is the explanation for this phenomenon? It is quite probable that the SH compound is gradually removed from the blood by (1) diffusion into the tissues or (2) oxidation to the disulphide (R·S —— S·R) form. In order to obtain evidence of this nature, use was made of the very sensitive reaction which these SH compounds yield with sodium nitroprusside and ammonia. A series of rats was injected with 75 c. c. M/100 sodium thioglycollate per kilo and the animals were bled (decapitation) at 1, 12, 30, and 60 minutes, respectively, following the injection. The blood so obtained was defibrinated with glass beads and the plasma separated by centrifugation. Normal plasma does not yield a purple color on the addition of sodium nitroprusside, ammonium sulphate crystals, and ammonia. The test is strongly positive with plasma obtained one minute after an injection of thioglycollate, and the intensity of the reaction gradually diminishes as the time interval between injection and bleeding is lengthened; and 60 minutes after the injection of the thioglycollate the test is very faint. There is, therefore, an excellent agreement between the intensity of the antagonistic action and that of the chemical test for the SH compound in the blood. Mention may also be made of the fact that the exsanguinated tissues of the animals injected with these SH compounds yield an unusually intense nitroprusside test shortly after the injection, an observation which clearly indicates that part of the SH compounds penetrates tissues with great ease.

The fact that defibrinated blood gradually destroys the SH group of thioglycollic acid was demonstrated by bleeding rats immediately after the injection of 75 c. c. M/100 sodium thioglycollate, defibrinating the blood with glass beads, and allowing this blood to stand at 20° C. in centrifuge tubes for varying lengths of time. The serum was then separated and tested with the nitroprusside reagent. It could thus be shown that the reaction became less intense as the time of standing of the blood was increased. After one hour the serum still gave a positive test, though considerably less intense than

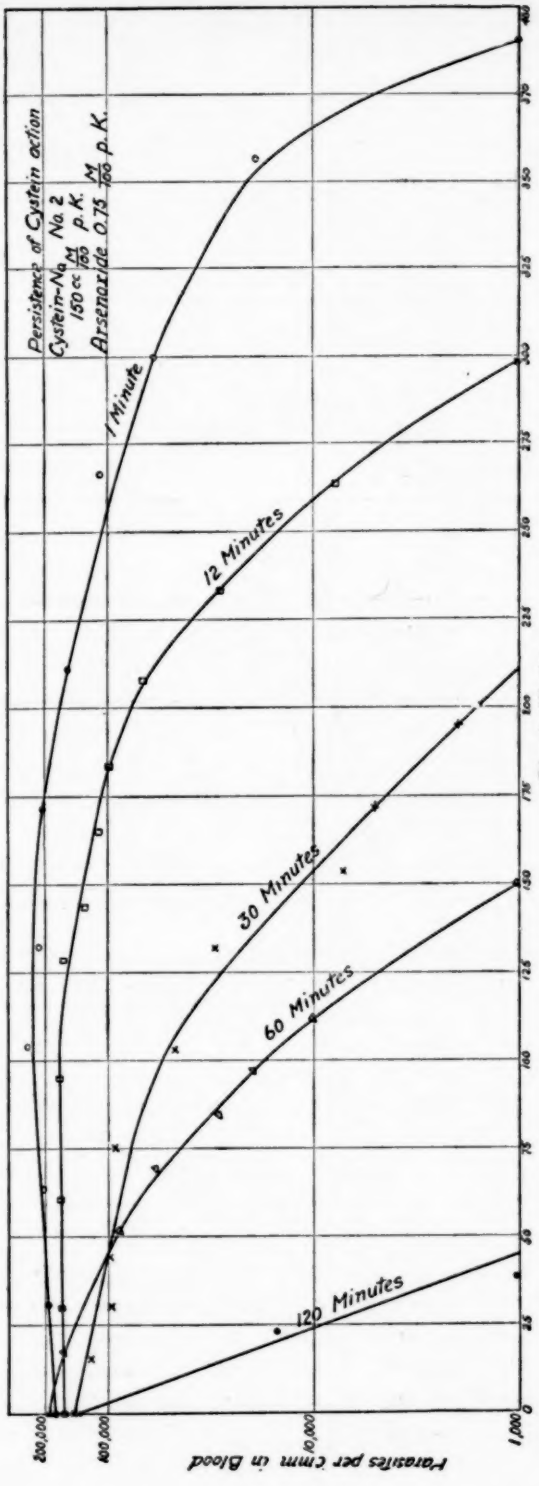

Persistence of Cystein action
Cystein-No. 2
150 cc M/100 p.K.
Arsenoxide 0.75 M/100 p.K.
1 Minute
12 Minutes
30 Minutes
60 Minutes
120 Minutes
Parasites per cmm in Blood
Time in Minutes
200,000
400,000
600,000
1,000
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
400

CHART 7.

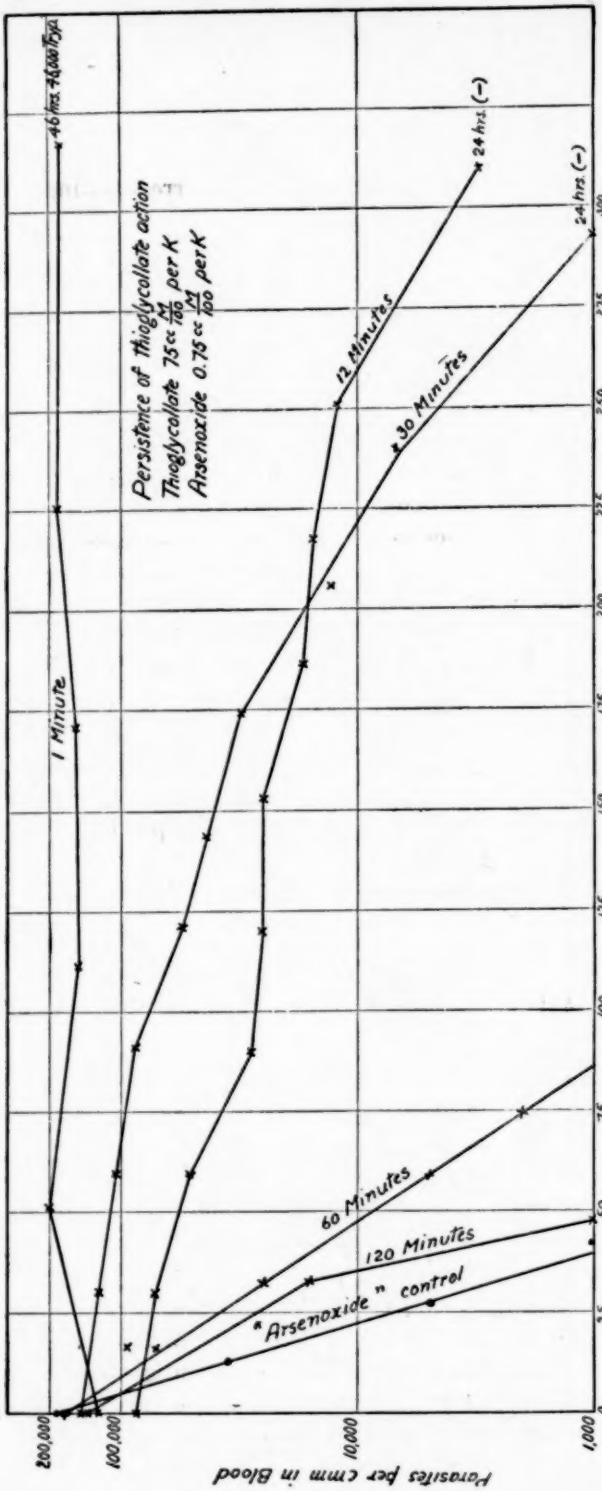

Persistence of Thioglycollate action
Thioglycollate 75 cc M/100 per K
Arsenoxide 0.75 cc M/100 per K
46 hrs. 45,000 Trypl.
24 hrs. (-)
24 hrs. (-)
12 Minutes
30 Minutes
1 Minute
60 Minutes
120 Minutes
"Arsenoxide" control
200,000
100,000
10,000
1,000
Trypl. per cmm in Blood
0
25
50
75
100
125
150
175
200
225
250
275
300
Time in Minutes

CHART 8.

the serum obtained one minute after the injection, and after two hours the test was very faint.

The conclusion is therefore justified that the gradual disappearance of the SH compound from the circulating blood is due partly to diffusion of the compound into the tissues and partly to oxidation within the blood, presumably to the corresponding disulphide (R·S —— S·R) modification.

Do trypanosomes contain sulphydryl compounds? So far it has tacitly been assumed that *Tr. equiperdum* contains glutathione or at least a closely related substance or substances containing an SH group. This assumption might seem quite justified in view of the fact that Gola (1902), Buffa (1904), Heffter (1908), and Hopkins (1922) have shown that all animal and vegetable cells with an active metabolism give the nitroprusside test. It is, of course, not feasable to attempt to isolate glutathione from trypanosomes on account of the enormous amount of material which would be required for this purpose. However, it seemed desirable at least to test trypanosomes by means of nitroprusside. For this purpose dogs were injected with this organism, and after a few days, when the parasites were quite numerous in the blood, the animals were bled into sodium citrate solution. The trypanosome layer was separated from the blood corpuscles and plasma by centrifugation, washed with physiological saline, and again centrifuged. The washing was repeated several times. The final sediment of almost pure white trypanosomes, on treatment with a little solid Na_2SO_4, a few drops of dilute nitroprusside and concentrated ammonia gave a typical purple reaction which faded out on standing. A positive nitroprusside test was also obtained from trypanosomes grown in rats. We conclude, therefore, that there can be little doubt of the presence of a substance in *Tr. equiperdum* which contains a SH group.

B. DETOXIFICATION OF ARSENOXIDE BY SH COMPOUNDS AS SHOWN IN RATS.

In a previous paper (Voegtlin and Thompson, 1922) it was shown that the arsenic of arsenoxide is tenaciously retained by the body of the albino rat. During the first 24 hours following the intravenous injection of 3 c. c. M/100 arsenoxide per kilo, only 19 per cent of the arsenic injected is excreted into the intestinal tract and with the urine. This fact and the observation that the drug disappears fairly rapidly from the blood were taken as evidence that arsenoxide has a great affinity for tissues.

As in the case of trypanosomes, it seems probable that glutathione or some other SH compounds of the tissues might react with arsenoxide, and this, of course, would reduce the amount of SH compounds in the tissues to such an extent that the latter would be

injured. It was therefore of interest to determine whether an extra supply of certain SH compounds would delay the onset of the toxic manifestations produced in rats by the injection of a toxic dose of arsenoxide.

The M L D of arsenoxide is 10 c. c. M/100 per kilo, if the drug is injected intravenously. (The majority of the animals injected with this dose die.) Immediate toxic symptoms appear always during the injection of this dose of arsenoxide, as pointed out by Voegtlin and Smith (1920) and Hunt (1921). These symptoms consist of struggling, convulsive movements, lashing of the tail, rigidity of the legs, irregular respiration with long pauses, protrusion of the eyes, lacrimation, salivation, and collapse, and several minutes later dilatation of the blood vessels of the ears. The animals then temporarily recover from the state of complete collapse and die within a short time. Practically the same symptoms are produced by sodium arsenite and other arsenicals of this type (R·As=O or R·As=S).

TABLE VI.—*The temporary antitoxic effect of sodium thioglycollate on the minimum lethal dose of "arsenoxide" in rats.*

"Arsenoxide" (10 c. c. M/100).		25 c. c. M/100 thioglycollate + "arsenoxide."		50 c. c. M/100 thioglycollate + "arsenoxide."	
Symptoms.	Time between dose of "arsenoxide" and death (*minutes*).	Symptoms.	Time between dose of "arsenoxide" and death (*minutes*).	Symptoms.	Time between dose of "arsenoxide" and death (*minutes*).
RAT NO. 1.		RAT NO. 2.		RAT NO. 3.	
Jerking, lashing tail, cessation of respiration, rigidity, and complete collapse during injection, followed by labored respiration, lacrimation, and, after 4 minutes, vaso-dilatation of ears. After 1 hour, ears normal color, depression, restlessness, diarrhea.	115	Very slight jerking at end of injection, followed by labored respiration, lacrimation, and salivation. After 8 minutes, dilatation of ear vessels. After 40 minutes, marked depression, restlessness, and partial collapse. After 70 minutes, complete collapse.	115	No reaction during injection, followed by labored respiration and lacrimation. After 10 minutes, dilation of ear vessels. After 30 minutes, lacrimation, salivation, and diarrhea. Then appeared normal for 48 hours.	4,200
RAT NO. 4.		RAT NO. 5.		RAT NO. 6.	
Same as rat No. 1.....	238	Same as rat No. 2.....	[1] S.	Same as rat No. 3. After 300 minutes, depression more marked. Slight convulsion and collapse. After 360 minutes, complete collapse.	540
RAT NO. 9.		RAT NO. 7.		RAT NO. 8.	
Same as rat No. 1.....	140	Same as rat No. 2. Then appeared normal for 48 hours.	4,200	Same as rat No. 3. After 300 minutes, depression more marked. Slight convulsions and collapse.	1,440

[1] Survival at least 1 week.

The course of events is completely altered when the injection of arsenoxide is preceded by a proper dose of a SH compound. In this case, the animals tolerate the injection of arsenoxide extremely well (with exception of lacrimation and salivation), and none of the other above-mentioned characteristic symptoms appear. Detoxification of the arsenic, however, is not permanent, and the animals ultimately die after a much longer time than in the case of the controls (Tables VI and VII).

Discussion.

The observations reported in this paper clearly indicate that certain SH compounds are able to counteract the toxic effect produced by arsenoxide on trypanosomes and a representative mammal. There are no obvious reasons to doubt that similar results could be obtained on other related forms of life. In view of the fact that SH compounds appear to occur as normal protoplasmic constituents of all living cells with an active metabolism and as R· As═══O compounds are highly toxic to most forms of life, it perhaps may be concluded that arsenic in this form can be regarded as a specific poison affecting the SH group of protoplasm.

It is quite likely that arsenoxide reacts chemically with the reduced form of glutathione and perhaps also with some other SH compounds which may occur in protoplasm [4] according to the following equation:

$$R\cdot As:O + \begin{matrix} HS\cdot R \\ HS\cdot R \end{matrix} = R\cdot As: \begin{matrix} S\cdot R \\ S\cdot R \end{matrix} + H_2O$$

or

$$R\cdot As: \begin{matrix} OH \\ OH \end{matrix} + \begin{matrix} HS\cdot R \\ HS\cdot R \end{matrix} = R\cdot As: \begin{matrix} S.R \\ S.R \end{matrix} + 2\ H_2O.$$

That similar compounds are formed with great ease in the test tube is shown by the formation of arsenic thioglycollate from As_2O_3 and thioglycollic acid. Reactions of this type would naturally reduce the concentration of the SH compounds of the cell in proportion to the amount of arsenoxide added. If the amount of arsenic furnished to the cell should exceed a certain limit, poisoning and death would necessarily follow as a result of the reduction of the absolute amount of SH compounds below the physiological requirement.

If, on the other hand, the cell is furnished with a certain extra supply of SH compounds, interaction between arsenic and SH compounds would then not lead to a reduction of the SH compounds below the physiological requirement, and the protoplasm would escape injury.

[4] Tanret (J. Pharm. Chim. 1909, VI series, XXX, 145) isolated from ergot ergothioneine which was shown by Barger and Ewing (J. Chem. Soc. 1911, *10*, 2336) to be a histidine derivative containing an SH group.

TABLE VII.—*Illustrates the temporary antitoxic effect and the ultimate increase in the toxicity of "arsenoxide" produced by sodium thioglycollate.*

Dose "arsenoxide," M/100 As equiv. soln. per K.	Sodium thioglycollate (C. C. M/100).				
	0	25	50	80	120
cc. 0.35					(−) S. (−) S. (−) S.
0.75				(−) S. (−) S. (−) S.	(−) S. (−) S. (−) D 1,140 min.
1.5				(−) S. (−) S. (−) S.	(−) D 150 (−) D 110 } Av., 126 min. (−) D 120
2.25				(−) S. (−) D 210 (−) D 200 } Av., 205 min.	S. (−) D 150 (−) D 135 } Av., 142 min.
3.5		(−) S. (−) S. (−) S.		(−) D 260 (−) D 230 } Av., 218 min. (−) D 165	(−) S. (−) D 390 min.
5.0		(−) S. (−) S. (−) S.	(−) S. (−) S. (−) S.	(−) D 5,940 (−) D 6,780 } Av., 6,060 min. (−) D 5,460	(−) D 6,960 (−) D 200 (−) D 240 } Av., 1,732 min. (−) D 360 (−) D 900

7.5	++ SSSS. ++ SSSS. ++ SSS. ++ SSS. ++ SSS. ++ SSS. ++ D.	+ D 4,140 (−) D 4,140 + D 4,800 } Av., 4,360 min.	D 1,200 D 4,080 D 4,200 } Av., 3,160 min.	(−) D 225 (−) D 3,180 (−) D 2,580 } Av., 1,995 min.	(−) D 3,840 (−) D 7,020 (−) D 270 (−) D 360 (−) D 360 (−) D 5,280 (−) D 840 (−) D 690 (−) D 1,440 } Av., 2,233 min.
10.0	+++ SSS. +++ DD 115 +++ DD 1,200 +++ DD 168 +++ DDD 120 +++ DDD 360 +++ DDDD 210 } Av., 328 min.	+ D 115 + D 4,800 + D 4,200 + D 4,200 (−) D 4,200 } Av., 3,503 min.	(−) D 540 (−) D 1,440 (−) D 4,440 D 4,080 (−) D 4,200 (−) D 4,200 } Av., 3,150 min.	(−) D 280 (−) D 110 (−) D 360 (−) D 240 (−) D 4,440 (−) D 88 } Av., 919 min.	+ D 150 + D 4,620 (−) D 4,620 (−) D 870 (−) D 630 } Av., 2,178 min.
15.0	+++ D 35 +++ D 15 +++ D 42 +++ D 38 +++ D 32 } Av., 32 min.	++ D 120 ++ D 43 ++ D 120 } Av., 94 min.		(−) D 80 (−) D 104 (−) D 114 } Av., 99 min.	(−) D 70 (−) D 5,400 (−) D 120 (−) D 180 (−) D 180 (−) D 5,880 (−) D 90 } Av., 1,702 min.
20.0					(−) D 240 (−) D 180 (−) D 180 (−) D 180 (−) D 840 } Av., 324 min.

D=death of one animal; S=survival at least 1 week; +++=severe "arsenoxide" symptoms; ++=marked "arsenoxide" symptoms; +=slight "arsenoxide" symptoms; (−)= absence of immediate "arsenoxide" symptoms.

The antagonism between SH compounds and arsenoxide is most pronounced on trypanosomes *in vitro*. Particular attention is called to the ratio of SH compound which will just detoxify arsenoxide. This ratio is, within a fairly wide range of variation in concentration, 1 to 10 or 1 to 20; i. e., 10 or 20 more molecules of SH compound are necessary to detoxify one molecule of arsenoxide. This may be explained by assuming that the medium in which the trypanosomes are suspended; i. e., blood, favors the auto-oxidation of the SH group. This is supported by observations described in the experimental part.

In order to antagonize arsenoxide with regard to its action on the trypanosomes in the circulating blood, still larger quantities of SH compound are needed, giving a ratio of 1 to 100 or even more, according to the SH compound used. We have shown that the SH compounds are to some extent withdrawn from the blood by the tissues; moreover, it is to be expected that blood at body temperature would accelerate the oxidation of the SH group, as compared with the rate of oxidation which obtains when the blood is kept in the test tube at about 20° C. The greater ratio between arsenoxide and SH compounds in the experiments in the living animal are therefore easily explained on the basis of the greater rate of oxidation of the SH group under these conditions. This is in perfect agreement with the generally accepted view that tissue processes always tend toward a dynamic equilibrium if one constituent of the system is present in excess. In fact, the experimental evidence presented in the paper is an excellent illustration of this view.

So far it has been assumed that the SH group of protoplasm, or that of a compound added to the living test object, reacts chemically with R · As$\equiv$0. We wish to emphasize in this place that this reaction may very well proceed in the reverse direction, especially as the excess of SH compound is gradually oxidized to the disulphide (R · S$\equiv$S · R) modification, otherwise the detoxification of the arsenoxide action on the rat would not be limited in time, but would be permanent, and the animal should survive the fatal dose.

As a matter of fact, we have good reason to treat this reaction between R · As$\equiv$0 and R · SH from the standpoint of a dynamic equilibrium, for life is essentially dependent on a dynamic and not on a static equlibrium of the constituents of protoplasm. It is therefore not astonishing that the cell should have the property of dissociating a reaction product of R · As$\equiv$0 with SH compounds into its components as soon as the excess of free SH compound has been oxidized.

Our experiments furnish substantial proof for the suggestion made by Meyer and Gottlieb that arsenic causes its toxic effect upon

protoplasm by reacting with a substance which is present in very small amounts (Minimalstoff).

It still remains to explain the difference in susceptibility of different types of cells to arsenic. We do not claim to have furnished any proof which would serve to elucidate this important question. However, our observations at least are suggestive. It might be reasonably assumed that trypanosomes are more easily killed than rats, for the reason that the former contain and are dependent on a smaller absolute amount of SH compounds than the vital organs of the higher animals. Exposure to a certain concentration of arsenoxide would therefore kill trypanosomes, whereas the infected animal would survive. There are other factors which very likely also enter into this problem, such as differences in the permeability for arsenic of trypanosomes on the one hand and tissue cells on the other.

A similar reasoning might also be applied to the unsolved problem of the specificity of the chemotherapeutic action of arsenicals for certain organisms. It is probable that the only infectious diseases that can be benefited by arsenic therapy are those whose causative agents are dependent on a considerable amount of SH compounds for their normal metabolism. It would be interesting, indeed, to attempt the treatment of tularæmia with arsenic, because Francis recently observed the interesting fact that *Bacterium tularense* grows particularly well in a culture medium containing cystine.[5]

So far we have dealt with the pharmacological significance of our observations, but we do not want to neglect the more fundamental biological bearing of the work.

The suggestion advanced by Heffter, that certain SH compounds are responsible for the reducing properties of tissues, has led to some very interesting experiments. Meyerhof (1918) has shown that extracts of yeast, made by extracting the latter with boiling water, restore "respiration" to washed acetone yeast in proportion to the intensity of the nitroprusside test given by the extracts. He, furthermore, showed that a similar effect could be produced on acetone or washed yeast, if thioglycollic or thiolactic acid were used in place of the yeast extract. Cystine, however, was without effect.

More recently, Hopkins (1921) has shown that pieces of various organs (liver, kidney, muscle) can oxidize the reduced form and reduce the oxidized form of glutathione.

Hopkins and Dixon (1922) observed that washed muscle has the power to reduce dithiodiglycollic acid to thioglycollic acid. The former substance promotes biological oxidations less effectively than the oxidized form of glutathione. These investigators reach the important conclusion that "coexisting in living tissues with the

[5] Tularæmia: X. The Amino-acid Cystine in the Cultivation of *Bacterium tularense*. By Edward Francis. Public Health Reports, vol. 38, No. 25, June 22, 1923, p. 1396.

special enzymic mechanism is a thermostable mechanism for oxidations and reductions. Materials in close association with structural elements are oxidized, aërobically or anaërobically, with the coagency of the sulphur group of glutathione."

These observations on washed yeast and surviving tissues clearly demonstrate that glutathione and certain other SH compounds (thiolactic and thioglycollic acids) are concerned in certain phases of biological oxidations and reductions.

If glutathione really plays such an important part in the life of the cell, then it is not at all surprising that substances such as arsenoxide, which react with the SH group of glutathione, should exert a toxic action, and that the latter should be counteracted by supplying the cell with an extra amount of glutathione. In the final analysis, arsenic would have to be considered as a poison which causes death of the cell by interfering with the oxidative processes governed by glutathione.

Conclusions.

1. Glutathione (reduced form), thioglycollic acid, α–thiolactic acid, glycylcystein, and thiosalicylic acid counteract the toxic action of R· As═O compounds on trypanosomes, both *in vitro* and in the circulating blood of infected rats.

2. The appearance of the symptoms produced by R · As═O compounds in rats is greatly delayed, as is also the time of death.

3. The corresponding disulphides (R · S—S · R) of the above-mentioned compounds are much less effective or practically without effect.

4. Amino-acids containing no SH group, glucose, lecithin, and inorganic salts, are without effect.

5. The antitoxic effect of SH compounds is therefore specifically due to the SH group.

6. Trypanosomes, as all cells with an active metabolism, contain an SH compound (possibly glutathione), as indicated by the characteristic nitroprusside test.

7. SH compounds injected intravenously are partly oxidized within the blood and diffuse in part into the tissues.

8. The theory is advanced that arsenic (in the form R · As═O) is a specific poison for the SH group of glutathione and possibly other SH compounds which may occur in protoplasm.

9. The bearing of these observations on the chemotherapeutic action of arsenic is pointed out.

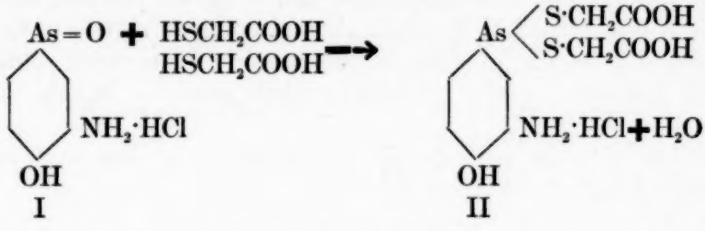
10. The findings furnish convincing additional proof of the biological importance of glutathione in the life of the cell.

References.

Buffa, Edward (1904): Jour. de Physiol. et Path. Gèn., VI., 645.
Cushny, Arthur R. (1918): A Textbook of Pharmacology and Therapeutics. Lea & Febiger, Philadelphia and New York.
Ehrlich, Paul (1910): Zeit. angew. Chem., XXIII, 2.
Fischer, Emil and Suzuki, U. (1904): Ber. deutsch. Chem. Gesell., XXXVII, 4575.
Gola, (1902): Malpighia, XVI.
Heffter, A. (1908): Med. Naturwiss. Arch., I, 81.
Hopkins, Frederick Gowland (1921): Biochem. Jour., XV, 286.
Hopkins, Frederick Gowland, and Dixon, M. (1922): Jour. Biol. Chem., LIV, 527.
Hunt, Reid (1921): Jour. Am. Med. Ass., LXXVI, 854.
Meyer, Hans H., and Gottlieb, R. (1922): Die experimentelle Pharmakologie. Urban & Schwarzenberg. Berlin and Vienna.
Meyerhof, O. (1918): Arch. Ges. Physiol., CLXX, 428.
Sollmann, Torald (1922): A Manual of Pharmacology and its Applications to Therapeutics and Toxicology. Philadelphia and London. W. B. Saunders Co.
Voegtlin, Carl, and Smith, Homer W. (1920): Jour. Pharmacol. Exp. Therap., XV, 475.
——— (1921): Ibid., XVI, 456.
Voegtlin, Carl, and Thompson, J. W. (1922): Jour. Pharmacol. Exp. Therap., XX, 85.

Addendum.

A new compound has been prepared by condensation of 3-amino-4-hydroxy-phenyl-arsenious-oxide (I) with thioglycollic acid. The compound which forms, even though four mols. of thioglycollic acid are supplied, appears to be one with two mols. of thioglycollic acid:



Analyses indicate that the complex closely approaches this formula (II).

CONDENSATION OF "ARSENOXIDE" AND THIOGLYCOLLIC ACID.

Seven grams of 3-amino-4-hydroxy-phenyl-arsenious-oxide hydrochloride are mixed with 11 gms. (4 mols.) of thioglycollic acid in a 100-c. c. flask. A red-brown color appears, and the reaction is exothermic. A slight frothing occurs, which may be due to occluded air or the driving off of the ½ mol. of bound alcohol held by the "arsenoxide." The reaction mixture is now heated on the boiling water bath for one hour, and becomes a clear, viscous, yellow fluid. Water resulting from the condensation is removed by placing the material in a vacuum desiccator for 48 hours. The

gummy mass is now washed several times with anhydrous ether, with thorough mixing, and is then dissolved in absolute alcohol, in which it is easily soluble. A small amount of unchanged "arsenoxide" remains undissolved and is filtered off. The alcohol is then evaporated in a vacuum desiccator for several days. The mass swells and dries to a yellow-brown solid, easily powdered. It is now washed several more times with absolute ether to remove excess thioglycollic acid and alcohol, and is again dried in a vacuum desiccator for several days. It swells and dries to a solid foam, which may be pulverized for analysis. Analyses for arsenic were by the Lehmann method.

Arsenic found = 17.58 per cent. Arsenic calculated for the 3-amino-4-hydroxy-phenyl-arsenious-bis-mono-thioglycollic acid compound, $C_{10}H_{13}O_5NClAsS_2$ = 18.70 per cent. As analyzed, the new compound was low in arsenic by 1.12 per cent, indicating a purity of 94.23 per cent.

Sulphur analyses resulted as follows: S found = 18.16 per cent; S calculated = 16 per cent. Sulphur was high by 2.16 per cent, equivalent to 6.21 per cent of thioglycollic acid in excess. As the washing of the compound with ether was very difficult on account of its gummy nature and its hygroscopicity, it is probable that a slight excess of thioglycollic acid remained, and the arsenic and sulphur analyses confirm this.

The new product is a fluffy, light-yellow-brown powder, insoluble in water, but extremely hygroscopic and going to a red-brown resin very rapidly in the presence of moist air. It is very soluble in alcohol, insoluble in ether, soluble in alkali, insoluble in cold mineral acids.

For injection in animals the compound was dissolved in and neutralized with 0.1 Normal alkali.

TRYPANOCIDAL ACTION.

This compound was tested as to its action curve in animals infected with trypanosomes. It was found that in equimolecular doses it showed a marked delay in parasiticidal action as compared with arsenoxide. These data will be included in a Hygienic Laboratory Bulletin which will be issued later. Here it is only desired to point out that the results add further proof to the theory of arsenic action as formulated in this paper.

DEATH RATES IN A GROUP OF INSURED PERSONS.

COMPARISON OF DEATH RATES FOR PRINCIPAL CAUSES OF DEATH, MAY AND JUNE, 1923, AND RATES FOR WHITE AND COLORED FOR FIRST SIX MONTHS OF 1921, 1922, AND 1923.

The accompanying tables are taken from the Statistical Bulletin of the Metropolitan Life Insurance Co. for July, 1923. They present the mortality experience of the industrial insurance department of the company for May and June, 1923, and a comparison of the rates for white and colored policyholders for the years 1921, 1922, and 1923. The rates are based on a strength of approximately 14,500,000 insured persons.

The death rate for this group of persons for June, 1923 (8.7 per 1,000), is stated to be the lowest ever recorded for that month. It shows a decline of 3.6 per cent as compared with June, 1922, and of 7.1 per cent as compared with May, 1923. With the exception of pneumonia, all of the diseases of primary numerical importance registered lower death rates than those recorded for June, 1922, and, excepting cancer, declines from the rates for May, 1923, are also shown.

Death rates (annual basis) for principal causes per 100,000 lives exposed, May and June, 1923, and June and year 1922.

Cause of death.	Death rate per 100,000 lives exposed.			
	June, 1923.	May, 1923.	June, 1922.	Year 1922.[1]
Total, all causes	865.7	932.1	898.4	877.2
Typhoid fever	4.2	2.9	5.2	5.6
Measles	14.2	16.5	7.5	4.3
Scarlet fever	4.2	5.4	2.4	4.8
Whooping cough	4.1	5.4	2.1	2.6
Diphtheria	8.9	9.8	11.0	17.8
Influenza	11.7	24.4	10.0	21.5
Tuberculosis (all forms)	119.3	121.8	132.7	113.4
Tuberculosis of respiratory system	108.7	111.9	118.6	102.9
Cancer	69.8	69.8	72.0	71.5
Diabetes mellitus	14.9	18.9	[2]	17.0
Cerebral hemorrhage	55.2	61.5	62.4	62.4
Organic diseases of heart	124.4	133.9	126.0	126.0
Pneumonia (all forms)	54.4	82.9	51.7	73.3
Other respiratory diseases	12.3	14.2	11.3	13.6
Diarrhea and enteritis	9.9	6.4	11.8	10.7
Bright's disease (chronic nephritis)	70.3	72.3	72.9	69.9
Puerperal state	17.5	19.3	20.4	18.9
Suicides	8.7	9.0	8.5	7.4
Homicides	6.3	5.3	5.7	6.2
Other external causes (excluding suicides and homicides)	62.3	57.9	62.8	57.7
Traumatism by automobile	15.5	13.1	13.6	13.5
All other causes	192.9	194.4	221.7	172.6

[1] Based on provisional estimate of lives exposed to risk in 1922. [2] Not available.

Notwithstanding the high gross death rate in this group in the early part of the year, extending through March, largely chargeable to the influenza outbreak, the drop in mortality during April, May, and June brought the death among the white policyholders during the first half of 1923 to only one-third of 1 per cent increase over that for the corresponding period of 1922, and the rate among the colored persons to an excess of 4.2 per cent over that for the corresponding period of the previous year.

Among the encouraging features of the health record for the first half of 1923 the outstanding item is stated to be the continued decline in the death rate for tuberculosis, which predicts a new low rate for this year. Other encouraging items are the decline in cancer mortality, the drop in the death rate for puerperal diseases, a comparatively low pneumonia death rate, despite the influenza epidemic, and a decrease in diphtheria mortality. The rates for measles and whooping cough, on the other hand, are much higher than those recorded for the first half of 1922, the rate for measles among the white persons of this group being more than double and among the colored six times the rate for the first half of last year.

It is stated that 241 deaths (3.3 per 100,000) were caused by alcoholism during the first six months of 1923, as compared with 133 deaths (2 per 100,000) from the same cause during the corresponding period of 1922. In addition to the number above, 20 deaths were reported from wood and denatured alcohol poisoning during the first half of the current year.

Death rates (annual basis) for principal causes per 100,000 persons exposed, for white and colored policyholders, first six months of 1921, 1922, and 1923.

[Industrial department, Metropolitan Life Insurance Co.]

Cause of death.	Death rates per 100,000 persons exposed.					
	White.			Colored.		
	January-June, 1923.	January-June, 1922.	January-June, 1921.	January-June, 1923.	January-June, 1922.	January-June, 1921.
All causes of death	926.1	923.0	872.9	1,552.5	1,489.5	1,396.2
Typhoid fever	3.2	3.2	3.8	6.0	6.3	6.9
Measles	13.1	6.4	5.4	11.6	2.0	2.6
Scarlet fever	6.4	7.1	10.3	1.3	.6	3.6
Whooping cough	5.5	2.7	4.7	7.9	3.5	7.8
Diphtheria and croup	17.7	19.9	26.4	6.3	8.1	6.2
Influenza	47.2	32.7	11.0	98.3	68.1	24.3
Meningococcus meningitis	.7	.7	1.1	.6	.6	1.0
Tuberculosis (all forms)	102.7	108.5	110.0	253.8	260.1	284.6
Tuberculosis of respiratory system	94.2	98.2	98.9	233.5	238.7	259.2
Tuberculosis of the meninges, etc	4.2	4.7	5.6	5.8	5.4	6.4
Other forms of tuberculosis	4.3	5.6	5.5	14.6	16.0	19.0
Cancer	71.4	74.5	71.7	69.2	70.2	69.7
Diabetes	19.7	[1]	[1]	17.0	[1]	[1]
Cerebral hemorrhage; apoplexy	62.5	65.8	60.6	101.6	101.2	92.1
Organic diseases of the heart	135.0	138.5	119.5	216.3	206.9	178.0
Total respiratory diseases	115.0	114.1	102.1	214.7	182.9	160.4
Bronchitis	6.7	7.1	6.6	10.6	12.4	12.7
Bronchopneumonia	35.9	35.8	30.9	51.6	44.4	39.9
Pneumonia, lobar and undefined	63.6	62.7	55.6	140.0	113.4	95.1
Other diseases of respiratory system	8.8	8.6	8.9	12.6	12.7	12.7
Diarrhea and enteritis	6.7	7.8	10.7	8.9	11.7	11.0
Under 2 years	3.2	3.6	4.0	2.3	3.0	2.4
2 years and over	3.5	4.2	6.7	6.6	8.7	8.6
Acute nephritis	5.3	5.6	5.5	15.2	18.1	16.8
Chronic nephritis	70.8	70.6	67.6	119.7	125.4	110.4
Total puerperal state	18.8	20.6	21.2	24.2	27.3	29.8
Puerperal septicemia	7.2	7.7	10.0	9.3	11.1	13.2
Puerperal albuminuria and convulsions	4.1	5.1	4.6	5.5	6.7	7.4
Other diseases of puerperal state	7.4	7.9	6.7	9.4	9.6	9.1
Total external causes	66.6	63.7	63.4	100.2	89.3	94.7
Suicides	8.3	8.3	7.9	4.9	5.0	5.4
Homicides	3.2	3.5	3.6	29.7	24.7	26.7
Accidental and unspecified violence	55.1	51.8	51.8	65.5	59.6	62.5
Accidental drowning	4.8	5.4	6.1	2.7	6.9	6.2
Automobile accidents	12.0	11.1	10.8	10.6	6.2	8.3
All other and ill-defined causes of death	157.9	180.6	177.7	279.8	307.0	296.4

[1] Not available.

DEATHS DURING WEEK ENDED AUGUST 4, 1923.

Summary of information received by telegraph from industrial insurance companies for week ending August 4, 1923, and corresponding week of 1922. (From the Weekly Health Index, August 11, 1923, issued by the Bureau of the Census, Department of Commerce.)

	Week ended Aug. 4, 1923.	Corresponding week, 1922.
Policies in force	54, 580, 305	50, 350, 086
Number of death claims	8, 873	7, 535
Death claims per 1,000 policies in force, annual rate	8.5	7.8

Deaths from all causes in certain large cities of the United States during the week ended August 4, 1923, infant mortality, annual death rate, and comparison with corresponding week of 1922. (From the Weekly Health Index, August 11, 1923, issued by the Bureau of the Census, Department of Commerce.)

City.	Week ended Aug. 4, 1923.		Annual death rate per 1,000, corresponding week, 1922.	Deaths under 1 year.		Infant mortality rate, week ended Aug. 4, 1923 [2]
	Total deaths.	Death rate.[1]		Week ended Aug. 4, 1923.	Corresponding week, 1922.	
Total	5,869	10.4	10.4	864	873	.....
Akron, Ohio	24	6.0	7.0	4	4	47
Albany, N. Y.[3]	33	14.7	10.3	1	3	22
Atlanta, Ga	63	14.7	14.7	10	9	.....
Baltimore, Md.[3]	181	12.2	14.0	24	49	71
Birmingham, Ala	61	16.2	13.4	12	8	.....
Boston, Mass	151	10.2	11.5	21	20	60
Bridgeport, Conn	16	5.8	9.4	4	5	55
Buffalo, N. Y	120	11.7	9.8	18	21	75
Cambridge, Mass	21	9.8	9.9	0	2	0
Camden, N. J.[3]	26	10.9	13.3	8	5	132
Chicago, Ill	537	9.7	8.4	77	78	.....
Cincinnati, Ohio	108	13.9	12.9	28	11	184
Cleveland, Ohio[3]	163	9.6	7.9	30	30	82
Columbus, Ohio	71	14.2	10.3	4	5	42
Dallas, Tex	55	16.2	14.6	5	14	.....
Dayton, Ohio	33	10.4	10.3	5	2	82
Denver, Colo	58	11.1	14.0	5	10	.....
Des Moines, Iowa	16	5.9	.....	0	.....	.....
Detroit, Mich	201	10.5	9.4	36	26	72
Duluth, Minn	23	11.3	.....	4	.....	91
Erie, Pa	12	5.6	11.4	2	3	41
Fall River, Mass.[3]	26	15.5	14.2	6	9	85
Flint, Mich	19	8.4	.....	2	.....	40
Fort Worth, Tex	29	10.5	11.4	5	4	.....
Grand Rapids, Mich	28	10.0	7.6	5	7	79
Houston, Tex	20	10.1	9.0	7	4	.....
Indianapolis, Ind	89	13.5	10.4	11	8	85
Jacksonville, Fla	24	12.5	15.5	2	7	.....
Jersey City, N. J	47	7.9	10.7	6	7	40
Kansas City, Kans	31	14.0	18.3	3	1	69
Kansas City, Mo	86	12.7	15.8	10	14	.....
Los Angeles, Calif	174	13.6	13.1	20	15	75
Louisville, Ky	67	13.6	9.1	12	9	129
Lowell, Mass	34	14.4	13.2	6	10	104
Lynn, Mass	16	8.1	.....	4	.....	105
Memphis, Tenn	57	17.5	18.0	10	7	.....
Milwaukee, Wis	84	9.0	9.1	17	11	84
Minneapolis, Minn	61	7.8	9.0	5	10	27
Nashville, Tenn.[3]	43	18.5	17.8	2	4	.....
New Bedford, Mass	26	10.4	11.9	8	4	125
New Haven, Conn	33	9.9	7.7	5	6	65
New Orleans, La	123	15.9	17.9	19	20	.....
New York, N. Y	944	8.3	9.5	122	171	49
Bronx Borough	94	5.8	8.2	8	11	28
Brooklyn Borough	301	7.3	8.8	41	57	44
Manhattan Borough	425	9.8	10.5	61	88	59
Queens Borough	82	8.0	9.6	8	9	43
Richmond Borough	42	17.2	12.6	4	6	73
Newark, N. J	91	10.8	8.9	16	12	75

[1] Annual rate per 1,000 population.
[2] Deaths under 1 year per 1,000 births—an annual rate based on deaths under 1 year for the week and estimated births for 1922. Cities left blank are not in the registration area for births.
[3] Deaths for week ended Friday, Aug. 3, 1923.

Deaths from all causes in certain large cities of the United States during the week ended August 4, 1923, infant mortality, annual death rate, and comparison with corresponding week of 1922. (From the Weekly Health Index, August 11, 1923, issued by the Bureau of the Census, Department of Commerce.)—Continued.

City	Week ended Aug. 4, 1923.		Annual death rate per 1,000, corresponding week, 1922.	Deaths under 1 year.		Infant mortality rate, week ended Aug. 4, 1923.
	Total deaths.	Death rate.		Week ended Aug. 4, 1923.	Corresponding week, 1922.	
Norfolk, Va	26	8.5	10.0	9	1	159
Oakland, Calif	35	7.8	7.2	4	0	51
Omaha, Nebr	41	10.5	11.7	9	6	97
Paterson, N. J	31	11.6	8.3	2	1	32
Philadelphia, Pa	365	9.9	9.6	45	66	58
Pittsburgh, Pa	148	12.6	12.1	36	29	125
Portland, Oreg	33	6.7	9.7	5	0	51
Providence, R. I	40	8.6	15.8	6	8	49
Richmond, Va	59	17.0	9.6	14	6	172
Rochester, N. Y	57	9.4	9.7	8	15	63
St. Louis, Mo	171	11.1	9.5	28	18	.....
St. Paul, Minn	43	9.3	11.3	5	3	46
Salt Lake City, Utah [3]	23	9.5	5.0	6	3	98
San Antonio, Tex	64	18.1	14.1	9	15	.....
San Francisco, Calif	121	11.7	11.0	9	7	54
Seattle, Wash	50	8.3	6.6	5	1	44
Spokane, Wash	18	9.0	11.5	2	1	44
Springfield, Mass	30	10.8	9.3	4	4	57
Syracuse, N. Y	36	10.2	8.9	7	4	91
Tacoma, Wash	19	9.7	.....	3	.....	75
Toledo, Ohio	60	11.7	9.2	4	4	40
Trenton, N. J	29	11.9	14.6	9	8	152
Utica, N. Y	16	8.1	.....	0	.....	0
Washington, D. C	122	14.5	11.7	18	10	103
Wilmington, Del	18	8.0	7.7	3	2	61
Worcester, Mass	26	7.1	10.8	4	6	46
Yonkers, N. Y	11	5.3	11.9	3	6	65
Youngstown, Ohio	29	11.4	8.3	6	4	81

[3] Deaths for week ended Friday, Aug. 3, 1923.

PREVALENCE OF DISEASE.

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring.

UNITED STATES.

CURRENT STATE SUMMARIES.

These reports are preliminary, and the figures are subject to change when later returns are received by the State health officers.

Reports for Week Ended Aug. 11, 1923.

ALABAMA.

	Cases.
Chicken pox	2
Diphtheria	20
Dysentery	28
Influenza	8
Malaria	245
Measles	123
Mumps	1
Pellagra	15
Pneumonia	18
Poliomyelitis	1
Scarlet fever	9
Tuberculosis	29
Typhoid fever	107
Whooping cough	36

ARIZONA.

Diphtheria	5
Measles	3
Pneumonia	1
Scarlet fever	4
Tuberculosis	6
Typhoid fever	3

ARKANSAS.

Cerebrospinal meningitis	1
Chicken pox	2
Diphtheria	3
Hookworm disease	1
Influenza	5
Malaria	474
Measles	61
Mumps	1
Ophthalmia neonatorum	1
Paratyphoid fever	3
Pellagra	19
Pneumonia	1
Scarlet fever	2
Smallpox	2

ARKANSAS—continued.

	Cases.
Trachoma	4
Tuberculosis	18
Typhoid fever	34
Whooping cough	21

CALIFORNIA.

Cerebrospinal meningitis:	
Merced County	1
San Francisco	1
Jaundice—Pasadena	2
Lethargic encephalitis—La Mesa	1
Poliomyelitis—Ontario	1
Smallpox	21
Typhoid fever	14

COLORADO.

(Exclusive of Denver.)

Diphtheria	6
Measles	15
Mumps	2
Scarlet fever	2
Tuberculosis	139
Typhoid fever	1

CONNECTICUT.

Chicken pox	6
Conjunctivitis (infectious)	1
Diphtheria	24
Dysentery (bacillary)	2
Influenza	1
Lethargic encephalitis	2
Malaria	1
Measles	18
Mumps	5
Pneumonia (lobar)	3
Poliomyelitis	2
Scarlet fever	17
Septic sore throat	5

CONNECTICUT—continued.

	Cases.
Tuberculosis (all forms)	36
Typhoid fever	9
Whooping cough	59

FLORIDA.

Anthrax	2
Cerebrospinal meningitis	3
Diphtheria	11
Influenza	6
Lethargic encephalitis	1
Malaria	36
Pneumonia	34
Scarlet fever	1
Typhoid fever	30

GEORGIA.

Chicken pox	2
Diphtheria	6
Hookworm disease	5
Malaria	35
Measles	27
Pellagra	1
Scarlet fever	1
Septic sore throat	1
Smallpox	1
Tuberculosis (all forms)	8
Typhoid fever	21
Whooping cough	5

ILLINOIS.

Cerebrospinal meningitis:	
Cook County (including Chicago)	2
Chicago	1
Diphtheria:	
Cook County (including Chicago)	56
Chicago	51
Scattering	34
Influenza	3
Pneumonia	88
Poliomyelitis:	
Chicago	2
Morgan County	1
Stephenson County	1
Scarlet fever:	
Cook County (including Chicago)	24
Chicago	22
Scattering	25
Smallpox	4
Typhoid fever:	
Chicago	11
Scattering	48
Whooping cough	173

INDIANA.

Diphtheria	40
Influenza	10
Measles	61
Pneumonia	1
Rabies in animals:	
Floyd County	1
Sullivan County	1
Scarlet fever	17
Smallpox	13
Tuberculosis	33
Typhoid fever	11

[1] Week ended Friday.

IOWA.

	Cases.
Diphtheria	5
Scarlet fever	15
Typhoid fever	2

KANSAS.

Chicken pox	2
Diphtheria	15
Dysentery (bacillary)	2
Influenza	5
Lethargic encephalitis	4
Measles	52
Mumps	3
Pellagra	1
Pneumonia	5
Poliomyelitis	11
Scarlet fever	32
Smallpox	1
Tuberculosis	30
Typhoid fever	43
Whooping cough	95

LOUISIANA.

Dengue	2
Diphtheria	17
Malaria	21
Measles	4
Scarlet fever	3
Smallpox	2
Tuberculosis	24
Typhoid fever	30
Whooping cough	1

MAINE.

Chicken pox	4
Diphtheria	7
German measles	2
Influenza	1
Measles	22
Mumps	3
Poliomyelitis	2
Scarlet fever	10
Tuberculosis	6
Typhoid fever	3
Whooping cough	10

MARYLAND.[1]

Cerebrospinal meningitis	1
Chicken pox	4
Diphtheria	20
Dysentery	19
Influenza	1
Malaria	4
Measles	56
Mumps	3
Ophthalmia neonatorum	2
Pneumonia (all forms)	11
Scarlet fever	31
Tetanus	1
Tuberculosis	37
Typhoid fever	44
Whooping cough	60

MICHIGAN.

Diphtheria	65
Measles	85
Pneumonia	18

MICHIGAN—continued.

	Cases.
Scarlet fever	51
Smallpox	9
Tuberculosis	46
Typhoid fever	22
Whooping cough	99

MINNESOTA.

Chicken pox	1
Diphtheria	44
Measles	12
Pneumonia	2
Poliomyelitis	2
Scarlet fever	56
Smallpox	11
Tuberculosis	56
Typhoid fever	11
Whooping cough	13

MISSISSIPPI.

Cerebrospinal meningitis	1
Diphtheria	15
Poliomyelitis	1
Scarlet fever	3
Smallpox	2
Typhoid fever	42

MISSOURI.

Cerebrospinal meningitis	2
Chicken pox	2
Diphtheria	33
Epidemic sore throat	1
Measles	39
Mumps	4
Ophthalmia neonatorum	1
Poliomyelitis	2
Scarlet fever	19
Smallpox	1
Tetanus	1
Trachoma	4
Tuberculosis	55
Typhoid fever	27
Whooping cough	131

MONTANA.

Diphtheria	2
Rocky Mountain spotted fever:	
Wolf Creek	1
Scarlet fever	6
Typhoid fever	2

NEW JERSEY.

Chicken pox	22
Diphtheria	58
Influenza	4
Malaria	1
Measles	36
Pneumonia	28
Poliomyelitis	7
Scarlet fever	17
Typhoid fever	22
Whooping cough	70

NEW MEXICO.

Chicken pox	2
Conjunctivitis	1
Diphtheria	16
Measles	4

NEW MEXICO—continued.

	Cases.
Scarlet fever	1
Smallpox	3
Tuberculosis	3
Typhoid fever	16
Whooping cough	4

NEW YORK.

(Exclusive of New York City.)

Cerebrospinal meningitis	1
Diphtheria	73
Influenza	1
Lethargic encephalitis	2
Measles	239
Pneumonia	58
Poliomyelitis	12
Scarlet fever	73
Smallpox	5
Typhoid fever	32
Whooping cough	162

NORTH CAROLINA.

Cerebrospinal meningitis	1
Chicken pox	6
Diphtheria	48
Measles	193
Scarlet fever	22
Smallpox	21
Trachoma	1
Typhoid fever	90
Whooping cough	156

OREGON.

Chicken pox	1
Diphtheria	5
Measles	7
Pneumonia	[1]3
Scarlet fever	8
Smallpox	7
Tuberculosis	2
Typhoid fever	3
Whooping cough	8

SOUTH DAKOTA.

Anthrax	1
Diphtheria	2
Measles	17
Pneumonia	1
Poliomyelitis	1
Scarlet fever	3
Tuberculosis	2
Typhoid fever	3
Whooping cough	2

TEXAS.

Chicken pox	6
Dengue	5
Diphtheria	18
Dysentery	6
Influenza	9
Measles	12
Mumps	11
Paratyphoid fever	2
Pellagra	6
Pneumonia	5
Poliomyelitis	1
Scarlet fever	17

[1] Deaths.

TEXAS—continued.

	Cases.
Smallpox	12
Trachoma	10
Typhoid fever	74
Tuberculosis	49
Whooping cough	28

VERMONT.

Chicken pox	3
Measles	37
Mumps	12
Poliomyelitis	4
Scarlet fever	2
Smallpox	3
Whooping cough	14

WASHINGTON.

Chicken pox	12
Diphtheria	20
Dysentery	3
Measles	16
Mumps	4
Pneumonia	1
Poliomyelitis:	
King County	1
Seattle	1
Whatcom County	1
Scarlet fever	22
Smallpox	16
Tuberculosis	58
Typhoid fever	10

WASHINGTON—continued.

	Cases.
Vincent's angina	1
Whooping cough	50

WEST VIRGINIA.

Diphtheria	3
Scarlet fever	11
Typhoid fever	5

WISCONSIN.

Milwaukee:	
Cerebrospinal meningitis	1
Chicken pox	1
Diphtheria	8
Poliomyelitis	2
Scarlet fever	8
Smallpox	1
Tuberculosis	15
Whooping cough	29
Scattering:	
Chicken pox	8
Diphtheria	46
Measles	105
Pneumonia	2
Scarlet fever	48
Smallpox	10
Tuberculosis	19
Typhoid fever	8
Whooping cough	150

WYOMING.

Measles	2
Tuberculosis	1

Reports for Week Ended August 4, 1923.

NORTH DAKOTA.

	Cases.
Chicken pox	3
Diphtheria	2
Lethargic encephalitis	2
Measles	23
Pneumonia	2
Poliomyelitis	2
Scarlet fever	2
Smallpox	2
Tuberculosis	2

NORTH DAKOTA—continued.

	Cases.
Typhoid fever	2
Whooping cough	1

WYOMING.

Measles	5
Scarlet fever	3
Smallpox	1
Tuberculosis	1
Typhoid fever	2

SUMMARY OF CASES REPORTED MONTHLY BY STATES.

The following summary of monthly State reports is published weekly and covers only those States from which reports are received during the current week:

State.	Cerebrospinal meningitis.	Diphtheria.	Influenza.	Malaria.	Measles.	Pellagra.	Poliomyelitis.	Scarlet fever.	Smallpox.	Typhoid fever.
June, 1923.										
Delaware	.....	16	4	5	71	.....	.....	33	.....	4
Montana	.....	12	.....	.....	101	.....	.....	60	25	2

CITY REPORTS FOR WEEK ENDED JULY 28, 1923.

CEREBROSPINAL MENINGITIS.

The column headed "Median for previous years" gives the median number of cases reported during the corresponding week of the years 1915 to 1922, inclusive. In instances in which data for the full eight years are incomplete, the median is that for the number of years for which information is available.

City.	Median for previous years.	Week ended July 28, 1923.	
		Cases.	Deaths.
Alabama:			
Birmingham	0	1	.....
California:			
Los Angeles	0	.....	1
Illinois:			
Chicago	1	1	.....
Freeport	0	.....	1
Springfield	0	1	.....
Kansas:			
Parsons	0	1	.....
Maryland:			
Baltimore	1	2	.....
Massachusetts:			
Lawrence	0	.....	1
Methuen	0	1	.....
Michigan:			
Ann Arbor	0	.....	1
Missouri:			
St. Louis	0	2	1
New Jersey:			
West Hoboken	0	1	.....
New York:			
Buffalo	0	1	.....
North Carolina:			
Winston-Salem	0	.....	1
Ohio:			
Columbus	0	1	.....
Pennsylvania:			
Philadelphia	1	.....	1
Pittston	0	1	.....
Wilkes-Barre	0	1	.....
West Virginia:			
Charleston	0	1	.....
Wisconsin:			
Milwaukee	1	2	.....

DIPHTHERIA.

See p. 1926: also Current State summaries, p. 1917, and Monthly summaries by States, p. 1920.

INFLUENZA.

City.	Cases.		Deaths, week ended July 28, 1923.
	Week ended July 29, 1922.	Week ended July 28, 1923.	
California:			
Los Angeles	1	5	.....
Oakland	.....	1	.....
San Diego	.....	1	.....
San Francisco	1	1	.....
Santa Barbara	.....	.....	1
Florida:			
Tampa	2	.....	.....
Georgia:			
Atlanta	1	.....	.....
Illinois:			
Chicago	.....	4	1
Maryland:			
Baltimore	.....	1	1
Cumberland	3	.....	.....
Massachusetts:			
Adams	2	.....	.....
Boston	.....	1	.....
Michigan:			
Detroit	.....	.....	1
New Jersey:			
Newark	5	.....	.....
New York:			
New York	7	8	.....
Ohio:			
Cleveland	.....	1	.....
Pennsylvania:			
Philadelphia	.....	2	1
Pittsburgh	.....	2	2
Utah:			
Salt Lake City	.....	.....	1
Wisconsin:			
Milwaukee	1	.....	.....

LETHARGIC ENCEPHALITIS.

City.	Cases.	Deaths.
California:		
San Francisco	1	1
New Jersey:		
Bayonne	1	.....

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

MALARIA.

City.	Cases.	Deaths.	City.	Cases.	Deaths.
Alabama:			Illinois:		
Birmingham	2		Chicago	1	1
Dothan	5		Louisiana:		
Mobile	3		New Orleans	1	
Tuscaloosa	3		Maryland:		
Arkansas:			Baltimore	1	
Little Rock	1		Michigan:		
California:			Detroit	1	
Long Beach	1		Rhode Island:		
San Francisco	1		Providence	1	1
Connecticut:			Tennessee:		
Hartford	1		Memphis	23	
Florida:			Nashville	1	
Tampa	4		Texas:		
Georgia:			Dallas		1
Albany	3	1	Fort Worth	1	
Augusta	7	1	Houston		1
Brunswick	8		San Antonio		1
Macon	6				
Rome	2				
Savannah	4	1			

MEASLES.

See p. 1926; also Current State summaries, p. 1917, and Monthly summaries by States, p. 1920.

PELLAGRA.

City.	Cases.	Deaths.	City.	Cases.	Deaths.
Alabama:			North Carolina:		
Birmingham	1	1	Wilmington		1
Mobile		1	South Carolina:		
Tuscaloosa	1		Columbia	1	1
Massachusetts:			Virginia:		
Peabody	1		Richmond		1

PNEUMONIA (ALL FORMS).

Alabama:			Illinois—Continued.		
Birmingham	7	6	East St. Louis	1	
Dothan	2		Freeport		1
Mobile		1	Jacksonville		1
California:			La Salle		1
Alameda	1		Peoria		1
Long Beach		3	Springfield	10	1
Los Angeles	18	11	Indiana:		
Pasadena	1		East Chicago		1
Sacramento		1	Fort Wayne		1
San Francisco		8	Indianapolis		3
Stockton		3	New Castle		1
Colorado:			Terre Haute		1
Denver		6	Kentucky:		
Connecticut:			Covington		1
Bridgeport		1	Lexington		3
Fairfield	1		Louisville	4	3
Hartford		2	Louisiana:		
New Haven	1		New Orleans		14
District of Columbia:			Maine:		
Washington		8	Bangor	1	
Florida:			Portland		1
Tampa		1	Maryland:		
Georgia:			Baltimore		12
Atlanta		14	Massachusetts:		
Illinois:			Amesbury		1
Aurora	2	1	Attleboro		1
Blue Island		1	Boston		10
Chicago	52	25	Chelsea		1
Cicero	1		Fall River		2
Decatur		2	Haverhill	1	

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

PNEUMONIA (ALL FORMS)—Continued.

City.	Cases.	Deaths.
Massachusetts—Continued.		
Lowell		1
Lynn		1
Medford		1
New Bedford		4
Salem		1
Somerville	1	
Springfield		1
Taunton		1
Worcester	5	1
Michigan:		
Detroit	25	20
Flint		1
Grand Rapids	1	
Hamtramck		1
Highland Park		1
Muskegon		1
Minnesota:		
Rochester		1
Missouri:		
Kansas City		4
St. Joseph		1
Montana:		
Missoula	1	
Nevada:		
Reno		1
New Hampshire:		
Concord		1
New Jersey:		
Hoboken		2
Jersey City	1	
Kearny	1	
Passaic		1
Paterson	2	
Perth Amboy		3
Plainfield		1
Trenton	1	
New York:		
Albany	10	
Auburn	3	
Buffalo	6	3
Elmira		1
Lackawanna	2	
New York	117	62
Niagara Falls		1
Peekskill		1
Poughkeepsie	2	1
Rochester	13	1
Schenectady		1
Syracuse	5	
Troy	2	
Watertown		1
Yonkers	1	
North Carolina:		
Winston-Salem		1
Ohio:		
Akron	1	
Ashtabula	1	
Barberton	1	
Cincinnati		3
Cleveland	13	5
Columbus		3
Dayton	1	
East Cleveland		1
East Youngstown		1
Middletown		1
Newark		1
Springfield		1
Toledo		3
Youngstown		5
Zanesville		1
Oregon:		
Portland		2
Pennsylvania:		
Philadelphia	37	23
Pittsburgh		20
Rhode Island:		
Providence		2
South Dakota:		
Sioux Falls		1
Texas:		
Beaumont		2
Dallas		1
El Paso		3
Fort Worth		3
Galveston		1
Houston		3
San Antonio		1
Utah:		
Salt Lake City		1
Virginia:		
Alexandria		1
Lynchburg		1
Norfolk		1
Petersburg		1
West Virginia:		
Huntington		2
Wisconsin:		
Janesville		1
Milwaukee		2
Racine		1
Sheboygan		1

POLIOMYELITIS (INFANTILE PARALYSIS).

The column headed "Median for previous years" gives the median number of cases reported during the corresponding week of the years 1915 to 1922, inclusive. In instances in which data for the full eight years are incomplete, the median is that for the number of years for which information is available.

City.	Median for previous years.	Week ended July 28, 1923.	
		Cases.	Deaths.
Alabama:			
Birmingham	0	1	
California:			
San Diego	0	1	1
Connecticut:			
Hartford	0	2	
New Haven	0	1	
Illinois:			
Chicago	5	2	
Indiana:			
Indianapolis	0	1	
Kansas:			
Lawrence		1	
Wichita	0	1	
Louisiana:			
New Orleans	0	1	
Maryland:			
Baltimore	1	1	

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

POLIOMYELITIS (INFANTILE PARALYSIS)—Continued.

City.	Median for previous years.	Week ended July 28, 1922. Cases.	Deaths.
Massachusetts:			
Boston	1	1	.....
Clinton	0	1	.....
Newton	0	1	1
Michigan:			
Detroit	0	1	1
Missouri:			
Springfield	0	.....	1
Nebraska:			
Omaha	0	3	.....
New Jersey:			
Long Branch	0	1	.....
New York:			
New York	5	35	2
Newburgh	0	3	.....
Ohio:			
East Cleveland	.....	1	.....
Pennsylvania:			
Erie	0	1	.....
Pittsburgh	0	1	.....
Washington:			
Seattle	0	1	.....

RABIES IN ANIMALS.

City.	Cases.
California:	
Long Beach	1
Los Angeles	21
Richmond	1
Massachusetts:	
Chelsea	2
Missouri:	
Kansas City	2
New Jersey:	
Bloomfield	1
Orange	1

SCARLET FEVER.

See p. 1926; also Current State summaries, p. 1917, and Monthly summaries by States, p. 1920.

SMALLPOX.

The column headed "Median for previous years" gives the median number of cases reported during the corresponding week of the years 1915 to 1922, inclusive. In instances in which data for the full eight years are incomplete, the median is that for the number of years for which information is available.

City.	Median for previous years.	Week ended July 28, 1923. Cases.	Deaths.
California:			
Los Angeles	0	9	.....
Pasadena	0	1	.....
Sacramento	0	1	.....
Florida:			
Tampa	0	1	.....
Georgia:			
Atlanta	4	17	.....
Illinois:			
Chicago	1	5	.....
Rock Island	0	1	.....
Urbana	.....	1	.....
Indiana:			
Gary	0	2	.....
Huntington	0	1	.....
Indianapolis	1	1	.....
Kokomo	0	1	.....
Muncie	0	5	.....
South Bend	0	1	.....
Iowa:			
Davenport	.....	.....	.....
Des Moines	.....	.....	.....
Kansas:			
Kansas City	0	1	.....
Maryland:			
Baltimore	0	1	.....
Michigan:			
Detroit	2	2	.....
Minnesota:			
Duluth	1	2	.....
Minnesota—Continued.			
Minneapolis	5	2	.....
St. Paul	2	1	.....
Winona	.....	.....	.....
Missouri:			
Joplin	0	1	.....
St. Louis	0	15	.....
North Carolina:			
Winston-Salem	0	1	.....
Ohio:			
Columbus	0	1	.....
Oregon:			
Portland	5	2	.....
Pennsylvania:			
Chester	0	1	.....
Tennessee:			
Knoxville	.....	.....	.....
Texas:			
Fort Worth	0	1	.....
Vermont:			
Burlington	0	1	.....
Virginia:			
Richmond	0	1	.....
Washington:			
Aberdeen	1	1	.....
Seattle	4	1	.....
Spokane	.....	.....	.....
Wisconsin:			
Kenosha	0	3	1
Waukesha	0	1	.....

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

TETANUS.

City.	Cases.	Deaths.	City.	Cases.	Deaths.
Connecticut:			Massachusetts:		
Danbury	1		Cambridge	1	
Florida:			New York:		
Tampa		1	New York	1	1
Georgia:			Yonkers	1	1
Savannah	1	1	North Carolina:		
Illinois:			Winston-Salem		1
Chicago	1		Pennsylvania:		
Indiana:			Philadelphia	1	1
Indianapolis		1	Tennessee:		
Kansas:			Nashville		1
Kansas City	1		Texas:		
Kentucky:			Fort Worth	1	1
Lexington	1		San Antonio		1
Maryland:			Utah:		
Baltimore		1	Salt Lake City		2

TUBERCULOSIS.

See p. 1926; also Current State summaries, p. 1917.

TYPHOID FEVER.

The column headed "Median for previous years" gives the median number of cases reported during the corresponding week of the years 1915 to 1922, inclusive. In instances in which data for the full eight years are incomplete, the median is that for the number of years for which information is available.

City.	Median for previous years.	Week ended July 28, 1923.		City.	Median for previous years.	Week ended July 28, 1923.	
		Cases.	Deaths.			Cases.	Deaths.
Alabama:				Kansas:			
Birmingham	6	10	1	Coffeyville	1	4	
Dothan		1	2	Hutchinson	0	1	
Montgomery	3	4		Kansas City	2	1	
Arkansas:				Wichita	3	1	
Fort Smith	0	7		Kentucky:			
Little Rock	1	4		Louisville	10	7	
North Little Rock	1	1		Owensboro	2	2	
California:				Louisiana:			
Long Beach	0	1		New Orleans	3	2	1
Los Angeles	3	5	2	Maine:			
Sacramento	0	2	1	Biddeford	0		1
San Bernardino	0	1		Portland	0	1	
San Francisco	2	1		Maryland:			
Colorado:				Baltimore	14	8	3
Denver	1	2		Massachusetts:			
Trinidad	2	3		Boston	5	3	
Connecticut:				Haverhill	0	1	
Danbury	0	2	1	Lawrence	1	4	
Meriden	0	2		Lowell	0	1	
New Haven	3	3		Lynn	1	2	
District of Columbia:				Newburyport	0	1	
Washington	7	5		Michigan:			
Georgia:				Ann Arbor	0	1	
Atlanta	2	6	2	Battle Creek	0	2	
Brunswick	0	2		Detroit	12	4	
Macon	2	2		Grand Rapids	1	1	
Rome	2	4		Minnesota:			
Savannah	3	2		St. Paul	1	1	
Illinois:				Missouri:			
Chicago	7	4	2	Kansas City	2	1	2
Urbana		1		St. Louis	7	4	
Indiana:				Montana:			
Anderson	0	1		Great Falls	1	1	
Fort Wayne	0		1	Nebraska:			
Indianapolis	3	1		Lincoln	0	1	
South Bend	0	1		New Jersey:			
Iowa:				Jersey City	0	2	
Sioux City	0	1		Morristown	0	1	1

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

TYPHOID FEVER—Continued.

City.	Median for previous years.	Week ended July 28, 1923.	
		Cases.	Deaths.
New Mexico:			
Albuquerque	0	1	1
New York:			
Albany	1	6	.....
Elmira	1	1	.....
Mount Vernon	0	1	.....
New York	32	16	2
Newburgh	0	1	.....
Peekskill	0	1	.....
Schenectady	0	1	.....
White Plains	0	1	.....
Yonkers	0	1	1
North Carolina:			
Greensboro	0	15	1
Raleigh	0	1	.....
Winston-Salem	4	1	1
Ohio:			
Akron	1	1	.....
Bellaire	0	1	.....
Chillicothe	0	1	.....
Cincinnati	1	3	.....
Cleveland	5	6	.....
Columbus	1	3	1
Dayton	3	11	.....
Fremont	0	1	.....
Marion	0	1	.....
New Philadelphia	0	1	.....
Newark	0	1	.....
Norwood	0	1	.....
Toledo	2	4	.....
Oklahoma:			
Tulsa	10	1	.....
Oregon:			
Portland	0	1	.....
Pennsylvania:			
Allentown	0	1	.....
Altoona	1	1	.....
Harrisburg	0	2	.....
Lancaster	0	1	.....
Monessen	0	1	.....
Philadelphia	13	10	2
Pennsylvania—Contd.			
Pittsburgh	4	8	.....
Pottsville	0	1	.....
Scranton	0	1	.....
Uniontown	0	1	.....
Wilkes-Barre	0	2	.....
Rhode Island:			
Providence	1	1	1
South Carolina:			
Charleston	4	2	.....
Columbia	1	2	.....
Greenville	3	3	.....
Tennessee:			
Memphis	4	28	2
Nashville	10	4	1
Texas:			
Corpus Christi	1	1	.....
El Paso	0	2	.....
Fort Worth	4	3	.....
Houston	2	2	1
Waco	1	1	.....
Utah:			
Provo	.....	1	.....
Virginia:			
Charlottesville	0	1	.....
Lynchburg	2	1	.....
Norfolk	4	8	.....
Richmond	4	3	.....
Roanoke	1	1	.....
Washington:			
Everett	0	3	.....
Tacoma	0	2	.....
West Virginia:			
Charleston	1	1	1
Huntington	5	2	1
Martinsburg	2	2	.....
Wisconsin:			
Marinette	0	3	.....
Milwaukee	1	1	.....
Oshkosh	0	1	1

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Alabama:										
Birmingham	178,806	72	1	.....	8	3	3	.....	9	4
Dothan	10,034	5	.....	.....	4	.....	1	.....	.....	.....
Mobile	60,777	16	.....	.....	1	.....	.....	.....	.....	.....
Montgomery	43,464	11	.....	.....	.....	.....	.....	.....	.....	.....
Arkansas:										
Little Rock	65,142	.....	1	.....	2	.....	.....	.....	1	.....
North Little Rock	14,048	.....	.....	.....	.....	.....	.....	.....	1	.....
California:										
Alameda	28,806	3	.....	.....	7	.....	.....	.....	.....	1
Berkeley	56,036	7	.....	.....	4	.....	.....	.....	.....	.....
Eureka	12,923	3	.....	.....	4	.....	.....	.....	2	.....
Glendale	13,536	10	.....	.....	.....	.....	.....	.....	1	1
Long Beach	55,593	18	5	.....	.....	.....	1	.....	3	.....
Los Angeles	576,673	192	59	1	40	1	12	.....	57	25
Oakland	216,261	.....	8	.....	7	1	6	.....	2	.....
Pasadena	45,354	14	1	.....	3	.....	1	.....	4	.....
Richmond	16,843	1	.....	.....	1	.....	.....	.....	.....	.....
Riverside	19,341	3	.....	.....	.....	.....	2	.....	4	.....
Sacramento	65,908	16	.....	.....	6	.....	.....	.....	.....	.....

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
California—Continued.										
San Bernardino	18,721	9	1		2		2			
San Diego	74,683	15	1		3				3	2
San Francisco	506,676	126	17	2	49	2	9		14	7
Santa Ana	15,485	10								
Santa Barbara	19,441	6								1
Santa Cruz	10,917	6								1
Stockton	40,296	17	1						3	2
Vallejo	21,107	0					3			
Colorado:										
Denver	256,491	73	9		5		2			10
Greeley	10,958	2		1						
Pueblo	43,050	10	5				3			1
Trinidad	10,906				1		1			
Connecticut:										
Bridgeport	143,555	15	4				8		7	1
Bristol	26,629	2								
Danbury (city)	18,943	4	1						1	
Derby	11,238	3								
Fairfield (town)	11,475	1	4				1		1	1
Hartford	138,036	29	2				1		9	1
Manchester (town)	18,379	2								
Meriden (city)	29,867				5				1	
New Haven	162,537	33	5						6	1
New London	25,688	21			1					
District of Columbia:										
Washington	437,571	119	4		12		2		23	16
Florida:										
St. Petersburg	14,237	4								
Tampa	51,608	9	1		1				4	2
Georgia:										
Albany	11,555				1					
Atlanta	200,616	95	3	1	3	1	4		4	
Augusta	52,548	10	2		4					
Brunswick	14,413	7							1	
Macon	52,995		1		6					
Rome	13,252				17		1			
Savannah	83,252	27			2	2			7	5
Idaho:										
Boise	21,393	4					1			
Illinois:										
Alton	24,682	4	1							
Aurora	36,397	8	1		1					
Bloomington	28,725	11			2					1
Blue Island	11,424	2	1		1					
Centralia	12,491	5								
Chicago	2,701,705	529	43	2	62	3	20		201	35
Cicero	44,995	7			1				1	1
Decatur	43,818	11	2		2				2	
East St. Louis	66,767	22			1					1
Elgin	27,454	7			4					
Evanston	37,234	7								
Freeport	19,669	4			1		1			
Galesburg	23,834	4								
Jacksonville	15,713	12							3	3
Kewanee	16,026	4								
La Salle	13,050	2							1	
Oak Park	39,858	8							4	
Peoria	76,121	15			1					
Quincy	35,978	12	1				1			
Rock Island	35,177	2			5				1	
Rockford	65,651	13	1		12					1
Springfield	59,183								1	
Urbana	10,244								1	
Indiana:										
Anderson	29,767				2					
Bloomington	11,595	2								
Crawfordsville	10,139	3								
East Chicago	35,967	8			2					
Elwood	10,790	1								
Fort Wayne	86,549	15	5				2		1	
Frankfort	11,585	3			2					
Gary	55,378	13					3			2
Hammond	36,004	9								
Huntington	14,000	3								

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Indiana—Continued.										
Indianapolis	314,194	100	3	.....	9	.....	2	.....	12	7
Kokomo	30,067	9	.....	.....	.....	.....	.....	.....	.....	2
La Fayette	22,486	4	.....	.....	1	.....	.....	.....	.....	.....
Logansport	21,626	6	.....	.....	.....	.....	.....	.....	.....	.....
Michigan City	19,457	2	.....	.....	.....	.....	.....	.....	.....	.....
Mishawaka	15,195	2	1	.....	1	.....	.....	.....	2	.....
Muncie	36,524	8	.....	.....	4	.....	.....	.....	.....	.....
Newcastle	14,458	3	.....	.....	.....	.....	.....	.....	.....	.....
South Bend	70,983	12	.....	.....	1	.....	6	.....	4	1
Terre Haute	66,083	25	1	.....	1	.....	1	.....	1	1
Iowa:										
Burlington	24,057	.....	1	.....	.....	.....	1	.....	2	.....
Cedar Rapids	45,566	.....	.....	.....	.....	.....	1	.....	.....	.....
Council Bluffs	36,162	8	1	.....	.....	.....	.....	.....	.....	.....
Iowa City	11,267	.....	.....	.....	.....	.....	1	.....	.....	.....
Marshalltown	15,731	.....	.....	.....	1	.....	2	.....	.....	.....
Muscatine	16,068	2	1	.....	.....	.....	.....	.....	1	.....
Sioux City	71,227	.....	3	.....	.....	.....	.....	.....	.....	.....
Waterloo	36,230	.....	.....	.....	.....	.....	1	.....	.....	.....
Kansas:										
Coffeyville	13,452	5	.....	.....	.....	.....	.....	.....	.....	.....
Fort Scott	10,693	3	.....	.....	1	.....	.....	.....	.....	.....
Kansas City	101,177	.....	.....	.....	7	.....	2	.....	6	.....
Lawrence	12,456	1	.....	.....	.....	.....	.....	.....	.....	.....
Topeka	50,022	7	.....	.....	12	.....	.....	.....	4	.....
Wichita	72,217	31	1	.....	10	.....	.....	.....	.....	.....
Kentucky:										
Covington	57,121	20	1	1	.....	.....	.....	.....	.....	2
Henderson	12,169	5	.....	.....	.....	.....	.....	.....	.....	.....
Lexington	41,534	15	.....	.....	1	.....	.....	.....	.....	2
Louisville	234,891	77	2	.....	1	.....	1	.....	14	5
Owensboro	17,424	.....	2	.....	.....	.....	.....	.....	3	.....
Louisiana:										
New Orleans	387,219	133	9	.....	.....	.....	.....	.....	15	14
Maine:										
Auburn	16,985	3	.....	.....	.....	.....	.....	.....	.....	1
Bangor	25,978	.....	.....	.....	2	.....	.....	.....	.....	.....
Bath	14,731	0	.....	.....	.....	.....	.....	.....	.....	.....
Biddeford	18,008	9	.....	.....	5	.....	.....	.....	.....	.....
Lewiston	31,791	8	.....	.....	.....	.....	1	.....	2	.....
Portland	69,272	24	2	.....	4	.....	1	.....	.....	2
Sanford (town)	10,691	4	.....	.....	.....	.....	.....	.....	.....	.....
Waterville	13,351	.....	1	.....	.....	.....	.....	.....	.....	.....
Maryland:										
Baltimore	733,826	184	10	2	66	.....	15	.....	58	21
Cumberland	29,837	8	.....	.....	.....	.....	2	.....	.....	.....
Frederick	11,066	2	.....	.....	1	.....	.....	.....	.....	.....
Massachusetts:										
Adams (town)	12,967	1	.....	.....	.....	.....	.....	3	.....	.....
Amesbury (town)	10,036	3	.....	.....	.....	.....	.....	.....	.....	.....
Arlington (town)	18,665	0	.....	.....	2	.....	.....	1	.....	.....
Attleboro	19,731	7	.....	.....	.....	.....	.....	.....	.....	2
Belmont (town)	10,749	2	.....	.....	1	.....	1	.....	1	.....
Beverly	22,561	3	.....	.....	.....	.....	.....	.....	.....	.....
Boston	748,060	167	39	2	36	2	30	1	37	11
Braintree (town)	10,580	2	2	.....	2	.....	.....	.....	.....	2
Brockton	66,254	10	4	.....	.....	.....	.....	.....	.....	.....
Brookline	37,748	2	1	.....	.....	.....	1	.....	.....	.....
Cambridge	109,694	24	7	.....	5	.....	.....	.....	3	2
Chelsea	43,184	11	.....	.....	3	.....	1	.....	2	.....
Chicopee	36,214	5	.....	.....	.....	.....	1	.....	.....	.....
Clinton	12,979	0	.....	.....	.....	.....	.....	.....	.....	.....
Dedham	10,792	0	.....	.....	.....	.....	.....	.....	.....	.....
Everett	40,120	4	3	.....	.....	.....	3	.....	1	.....
Fall River	120,485	30	3	.....	2	.....	1	.....	4	3
Framingham	17,033	6	.....	.....	3	.....	.....	.....	.....	.....
Gardner	16,971	5	1	1	.....	.....	.....	.....	1	.....
Greenfield	15,462	2	.....	.....	.....	.....	.....	.....	.....	.....
Haverhill	53,884	8	.....	.....	3	.....	2	.....	.....	1
Holyoke	60,203	14	2	.....	.....	.....	.....	.....	.....	.....
Lawrence	94,270	18	2	.....	4	.....	.....	.....	4	2
Leominster	19,744	5	.....	.....	2	.....	.....	.....	.....	.....
Lowell	112,759	20	.....	.....	2	.....	.....	.....	1	1
Lynn	99,148	13	1	.....	.....	.....	6	.....	3	1

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Massachusetts—Continued.										
Malden	49,103	8	2				2			3
Medford	39,038	3	2		2		1			
Melrose	18,204	3			1				1	
Methuen	15,189	0								
Milford	13,471	4							1	
New Bedford	121,217	25	5						8	3
Newburyport	15,618	5								
Newton	46,054	9	2		1		1		3	2
North Adams	22,282	2					1		2	
Northampton	21,951						1		1	
Peabody	19,552	3	1							
Pittsfield	41,763	5	1				1			
Plymouth	13,045	2								
Quincy	47,876	13	1				2		3	
Salem	42,529	2	2				2		2	1
Somerville	93,091	10	1		1				1	1
Southbridge	14,245	0	1		2					
Springfield	129,614	34			1		3		3	
Taunton	37,137	12								
Wakefield	13,025	0							3	
Waltham	30,915	5	2		2		1			
Watertown	21,457	3			2					
Webster	13,258	2								1
West Springfield	13,443	1								
Westfield	18,604	3							1	
Winthrop	15,455	1	2		1		1			1
Worcester	179,754	43	7	2	3	1			8	1
Michigan:										
Ann Arbor	19,516	18	1		1		1			
Battle Creek	36,164	1	1	1	2					
Benton Harbor	12,233	7	2							1
Detroit	993,678	215	19	2	28	3	33	1	47	23
Flint	91,599	17	3		17		2		2	1
Grand Rapids	137,634	15	2		9		4		1	
Hamtramck	48,615	6	1							1
Highland Park	46,499	15			4		2		2	
Holland	12,183		2							
Kalamazoo	48,487	14	3		14				1	1
Marquette	12,718	3					1			
Muskegon	36,570	12	3		1					
Pontiac	34,273	9					3			
Port Huron	25,944	2			8		1			
Sault Ste. Marie	12,096	2			1					
Minnesota:										
Duluth	98,917	17	3		1		4		2	2
Minneapolis	380,582	80	11		2		10		18	7
Rochester	13,722	23			2					
St. Paul	234,698	49	11		2		6	1	8	2
Missouri:										
Cape Girardeau	10,252	5								
Independence	11,686		1							
Kansas City	324,410	84	9	2	2	1	3		5	2
St. Joseph	77,939	26	1		2					
St. Louis	772,897	164	13	1	4		10		44	9
Springfield	39,631	19								1
Montana:										
Billings	15,100	2								
Great Falls	24,121	10	1		1					
Helena	12,037	5	1	1	2					
Missoula	12,668	3					1			
Nebraska:										
Lincoln	54,948	12			1					
Omaha	191,601	35	5							2
Nevada:										
Reno	12,016	3								
New Hampshire:										
Concord	22,167	5			4		1			1
Dover	13,029	2								
Keene	11,210	3			10					
New Jersey:										
Asbury Park	12,400	4			1					
Bayonne	76,754				2		1		4	
Belleville	15,660				1					
Bloomfield	22,019	3					2			
Clifton	26,470	5							1	

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
New Jersey—Continued.										
East Orange	50,710	4	2	.....	1	.....	.....	.....	2	.....
Garfield	19,381	1	.....	.....	.....	.....	.....	.....	.....	.....
Harrison	15,721	.....	1	.....	.....	.....	.....	.....	.....	.....
Hoboken	68,166	15	2	.....	1	.....	.....	.....	2	.....
Jersey City	298,103	.....	.....	.....	.....	.....	3	.....	8	.....
Kearny	26,724	1	1	.....	.....	.....	.....	.....	.....	.....
Long Branch	13,521	2	.....	.....	2	.....	.....	.....	.....	.....
Morristown	12,548	2	.....	.....	.....	.....	.....	.....	.....	.....
Orange	33,268	4	.....	.....	.....	.....	.....	.....	2	.....
Passaic	63,841	16	2	.....	4	.....	1	1	2	2
Paterson	135,875	.....	3	.....	9	.....	.....	.....	12	.....
Perth Amboy	41,707	4	.....	.....	.....	.....	.....	.....	1	.....
Plainfield	27,700	7	.....	.....	.....	.....	.....	.....	.....	1
Rahway	11,042	.....	1	.....	1	.....	1	.....	2	.....
Summit	10,174	0	.....	.....	.....	.....	.....	.....	.....	1
Trenton	119,289	31	9	1	1	.....	1	.....	2	3
West Hoboken	40,074	4	.....	.....	.....	.....	.....	.....	.....	.....
West New York	29,926	6	4	.....	.....	.....	1	.....	1	1
West Orange	15,573	3	.....	.....	1	.....	.....	.....	.....	.....
New Mexico:										
Albuquerque	15,157	6	3	.....	1	.....	.....	.....	3	.....
New York:										
Albany	113,344	.....	5	.....	16	.....	5	.....	13	.....
Amsterdam	33,524	4	2	.....	4	.....	.....	.....	.....	.....
Auburn	36,192	4	.....	.....	.....	.....	.....	.....	.....	1
Buffalo	506,775	109	6	.....	4	.....	5	.....	28	11
Cohoes	22,987	5	1	.....	4	.....	.....	.....	.....	1
Cortland	13,294	5	.....	.....	5	.....	1	.....	.....	.....
Elmira	45,393	12	1	.....	.....	.....	.....	.....	.....	.....
Geneva	14,648	2	.....	.....	.....	.....	.....	.....	.....	.....
Glens Falls	16,638	2	.....	.....	.....	.....	.....	.....	.....	.....
Hornell	15,025	4	.....	.....	3	.....	.....	.....	.....	.....
Hudson	11,745	2	.....	.....	.....	.....	.....	.....	.....	1
Ithaca	17,004	5	4	.....	.....	.....	.....	.....	.....	.....
Lackawanna	17,918	3	2	.....	11	.....	1	.....	2	.....
Little Falls	13,029	4	.....	.....	.....	.....	.....	.....	.....	.....
Lockport	21,308	4	.....	.....	.....	.....	.....	.....	1	.....
Mount Vernon	42,726	.....	1	.....	.....	.....	.....	.....	.....	.....
New York	5,620,048	1,063	117	9	99	3	39	2	[1] 207	[1] 89
Newburgh	30,366	10	.....	.....	1	.....	.....	.....	2	1
Niagara Falls	50,760	10	2	.....	4	.....	2	.....	2	1
North Tonawanda	15,482	2	.....	.....	2	.....	1	.....	.....	.....
Olean	20,506	6	.....	.....	.....	.....	4	.....	.....	.....
Peekskill	15,868	6	.....	.....	.....	.....	1	.....	1	.....
Poughkeepsie	35,000	9	.....	.....	.....	.....	2	.....	2	1
Rochester	295,750	56	3	1	8	.....	4	.....	10	2
Rome	26,341	9	1	.....	9	.....	2	.....	.....	1
Saratoga Springs	13,181	2	.....	.....	.....	.....	1	.....	3	.....
Schenectady	88,723	11	8	.....	17	.....	1	.....	4	1
Syracuse	171,717	25	2	.....	16	1	4	.....	5	1
Troy	72,013	18	.....	.....	4	.....	.....	.....	1	1
Watertown	31,285	8	.....	.....	12	.....	.....	.....	.....	.....
White Plains	21,031	4	.....	.....	.....	.....	1	.....	.....	.....
Yonkers	100,176	13	3	.....	.....	.....	.....	.....	.....	.....
North Carolina:										
Durham	21,719	2	.....	.....	.....	.....	.....	.....	3	.....
Greensboro	43,525	8	.....	.....	.....	.....	1	.....	.....	.....
Raleigh	24,418	13	.....	.....	.....	.....	.....	.....	.....	2
Rocky Mount	12,742	6	.....	.....	.....	.....	.....	.....	.....	.....
Salisbury	13,884	3	.....	.....	.....	.....	.....	.....	.....	.....
Wilmington	33,372	9	1	.....	.....	.....	.....	.....	.....	.....
Winston-Salem	48,395	24	.....	1	23	1	.....	.....	6	2
North Dakota:										
Fargo	21,961	7	.....	.....	.....	.....	.....	.....	.....	.....
Ohio:										
Akron	208,435	18	.....	.....	1	.....	2	.....	4	.....
Alliance	21,603	3	.....	.....	.....	.....	1	.....	1	.....
Ashtabula	22,082	5	.....	.....	1	.....	.....	.....	1	.....
Barberton	18,811	3	.....	.....	.....	.....	.....	.....	.....	.....
Bellaire	15,061	1	.....	.....	.....	.....	1	.....	1	.....
Bucyrus	10,425	1	.....	.....	.....	.....	.....	.....	1	.....
Cambridge	13,104	2	1	.....	.....	.....	.....	.....	1	.....
Chillicothe	15,831	6	.....	.....	.....	.....	.....	.....	.....	.....

[1] Pulmonary only.

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Ohio—Continued.										
Cincinnati	401,247	111	2	1	25	1	1	.....	12	16
Cleveland	796,841	142	16	1	33	.....	16	.....	34	18
Cleveland Heights	15,236	.....	.....	.....	.....	.....	.....	.....	1	.....
Columbus	237,031	66	6	.....	1	.....	.....	.....	7	8
Coshocton	10,847	.....	.....	.....	.....	.....	1	.....	.....	.....
Dayton	152,559	31	1	.....	.....	.....	4	.....	1	.....
East Cleveland	27,292	3	1	.....	.....	.....	.....	.....	1	.....
East Youngstown	11,237	2	.....	.....	.....	1	.....	.....	.....	.....
Findlay	17,021	4	.....	.....	1	.....	.....	.....	1	.....
Fremont	12,468	1	.....	.....	.....	.....	.....	.....	.....	.....
Hamilton	39,675	12	.....	.....	.....	.....	.....	.....	1	.....
Lancaster	14,706	7	3	.....	.....	.....	.....	1	4	.....
Lorain	37,295	.....	1	.....	1	.....	3	.....	2	.....
Marion	27,891	.....	.....	.....	.....	.....	1	.....	.....	.....
Martins Ferry	11,634	3	.....	.....	.....	.....	.....	.....	.....	.....
Middletown	23,594	9	.....	.....	.....	.....	.....	.....	.....	2
New Philadelphia	10,718	.....	.....	.....	1	.....	.....	.....	1	.....
Newark	26,718	3	.....	.....	.....	.....	.....	.....	.....	.....
Niles	13,080	2	.....	.....	1	.....	.....	.....	.....	.....
Norwood	24,966	4	.....	.....	.....	.....	.....	.....	.....	.....
Piqua	15,044	2	.....	.....	.....	.....	1	.....	3	.....
Salem	10,305	9	.....	.....	2	.....	.....	.....	.....	.....
Sandusky	22,897	7	.....	.....	.....	.....	1	.....	2	.....
Springfield	60,840	15	1	.....	.....	.....	.....	.....	.....	.....
Steubenville	28,508	8	1	.....	.....	.....	2	.....	1	.....
Tiffin	14,375	3	.....	.....	.....	.....	.....	.....	.....	.....
Toledo	243,164	44	3	.....	3	.....	6	.....	13	3
Youngstown	132,358	.....	5	.....	3	.....	5	1	.....	2
Zanesville	29,569	9	.....	.....	.....	.....	.....	.....	.....	.....
Oklahoma:										
Tulsa	72,075	.....	1	.....	.....	.....	.....	.....	.....	.....
Oregon:										
Portland	258,288	63	1	.....	4	.....	2	1	6	2
Pennsylvania:										
Allentown	73,502	.....	2	.....	.....	.....	.....	.....	.....	.....
Altoona	60,331	.....	1	.....	1	.....	1	.....	.....	.....
Ambridge	12,730	.....	.....	.....	1	.....	.....	.....	.....	.....
Bethlehem	50,358	.....	.....	.....	.....	.....	.....	.....	3	.....
Braddock	20,879	.....	.....	.....	1	.....	1	.....	.....	.....
Bradford	15,525	.....	.....	.....	2	.....	1	.....	.....	.....
Butler	23,778	.....	.....	.....	1	.....	.....	.....	.....	.....
Canonsburg	10,632	.....	1	.....	.....	.....	.....	.....	.....	.....
Carnegie	11,516	.....	1	.....	.....	.....	.....	.....	.....	.....
Chester	58,030	.....	2	.....	1	.....	.....	.....	.....	.....
Coatesville	14,515	.....	.....	.....	.....	.....	.....	.....	3	.....
Erie	93,372	.....	.....	.....	10	.....	.....	.....	6	.....
Farrell	15,586	.....	1	.....	.....	.....	3	.....	.....	.....
Greensburg	15,033	.....	2	.....	.....	.....	.....	.....	.....	.....
Harrisburg	75,917	.....	3	.....	3	.....	.....	.....	.....	.....
Homestead	20,452	.....	1	.....	.....	.....	.....	.....	.....	.....
Johnstown	67,327	.....	7	.....	3	.....	.....	.....	.....	.....
Lancaster	53,150	.....	1	.....	1	.....	.....	.....	1	.....
Lebanon	24,643	.....	6	.....	.....	.....	.....	.....	.....	.....
McKees Rocks	16,713	.....	1	.....	.....	.....	.....	.....	.....	.....
McKeesport	46,781	.....	.....	.....	2	.....	.....	.....	1	.....
Meadville	14,568	.....	.....	.....	5	.....	.....	.....	.....	.....
Monessen	18,179	.....	1	.....	.....	.....	.....	.....	.....	.....
Mount Carmel	17,469	.....	1	.....	2	.....	.....	.....	1	.....
Oil City	21,274	.....	1	.....	2	.....	.....	.....	.....	.....
Philadelphia	1,823,779	422	36	3	12	.....	10	.....	58	34
Pittsburgh	588,343	133	5	1	14	.....	12	2	13	16
Plymouth	16,500	.....	1	.....	.....	.....	.....	.....	.....	.....
Pottsville	21,876	.....	.....	.....	1	.....	.....	.....	.....	.....
Reading	107,784	.....	.....	.....	1	.....	.....	.....	1	.....
Scranton	137,783	.....	.....	.....	3	.....	.....	.....	.....	.....
Sharon	21,747	.....	.....	.....	1	.....	1	.....	.....	.....
Shenandoah	24,726	.....	3	.....	.....	.....	.....	.....	.....	.....
Steelton	13,428	.....	1	.....	.....	.....	1	.....	.....	.....
Swissvale	10,908	.....	1	.....	.....	.....	.....	.....	1	.....
Uniontown	15,692	.....	.....	.....	3	.....	.....	.....	.....	.....
Washington	21,480	.....	1	.....	2	.....	1	.....	.....	.....
Wilkes-Barre	73,833	.....	2	.....	2	.....	.....	.....	1	.....
Wilkinsburg	24,403	.....	3	.....	.....	.....	.....	.....	.....	.....
Williamsport	36,198	.....	1	.....	8	.....	1	.....	6	.....
York	47,512	.....	.....	.....	.....	.....	.....	.....	1	.....

CITY REPORTS FOR WEEK ENDED JULY 28, 1923—Continued.

DIPHTHERIA, MEASLES, SCARLET FEVER, AND TUBERCULOSIS—Continued.

City.	Population Jan. 1, 1920.	Total deaths from all causes.	Diphtheria.		Measles.		Scarlet fever.		Tuberculosis.	
			Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.
Rhode Island:										
Cranston	29,407	9							1	1
Cumberland (town)	10,077	0	1							
Newport	30,255	5	1				3			
Pawtucket	64,248	16					1			
Providence	237,595	66	2		1		4			1
South Carolina:										
Charleston	67,957	24			3				2	1
Columbia	37,524	17	1		1				1	2
Greenville	23,127	5			1					
South Dakota:										
Sioux Falls	25,202	8			8					
Tennessee:										
Chattanooga	57,895	0	2							
Memphis	162,351	65							11	4
Nashville	118,342	42	2				1		9	4
Texas:										
Amarillo	15,494	9					1		1	
Beaumont	40,422	16								2
Corpus Christi	10,522	2							1	
Dallas	158,976	54	2		1		2		1	1
El Paso	77,560	25							4	5
Fort Worth	106,482	22			3		1			1
Galveston	44,255	7								
Houston	138,276	43	3				1			1
San Antonio	161,379				1		1		3	11
Waco	38,500	6								1
Utah:										
Provo	10,303	2	1		2					
Salt Lake City	118,110	24	2		2		2			1
Vermont:										
Burlington	22,779	9			3					1
Virginia:										
Alexandria	18,060	5			2		1		1	1
Charlottesville	10,688	4	1				3			
Danville	21,539	8	3	1	2				1	1
Lynchburg	30,070	12			1				1	
Norfolk	115,777				10				4	3
Petersburg	31,012	16			2				1	1
Richmond	171,667	53	1		28				6	3
Roanoke	50,842	17			2	1	1		1	2
Washington:										
Bellingham	25,585				1					
Everett	27,644				1					
Seattle	315,312		3		11		1		5	
Tacoma	96,965		3				2			
Walla Walla	15,503								1	
West Virginia:										
Charleston	39,608	22			2					2
Clarksburg	27,869	1			11					
Huntington	50,177	24					1		4	1
Parkersburg	20,050	4								1
Wheeling	56,208	15			2		7		1	2
Wisconsin:										
Appleton	19,561	1								
Ashland	11,334	3					1			
Beloit	21,284	4					2		1	
Eau Claire	20,906				7				1	
Fond du Lac	23,427	5	1						2	1
Green Bay	31,017		2				3			
Janesville	18,293	5					1			
Kenosha	40,472	8	1				1		1	
La Crosse	30,421				1		1		2	
Madison	38,378				8		1			
Marinette	13,610				4					
Milwaukee	457,147	88	5		3		11		12	8
Oshkosh	33,162	8							1	
Racine	58,593	15					2			
Sheboygan	30,955	10	9				1		2	
Superior	39,671	10								1
Waukesha	12,558				1		2		2	
Wausau	18,661		3		2		2			
West Allis	13,745		3		1				1	

FOREIGN AND INSULAR.

BRAZIL.

Yellow Fever—Bahia.

During the week ended June 16, 1923, four cases of yellow fever with one death were reported at Bahia, Brazil.

BULGARIA.

Lethargic Encephalitis—Sofia.

During the period April 22 to May 12, 1923, two cases of lethargic encephalitis were reported at Sofia, Bulgaria.

CANADA.

Communicable Diseases—Ontario—July, 1923 (Comparative).

Communicable diseases have been notified in the Province of Ontario, Canada, as follows:

Disease.	July, 1923.		July, 1922.	
	Cases.	Deaths.	Cases.	Deaths.
Cerebrospinal meningitis	5	3	6	5
Chancroid	1		3	
Diphtheria	225	24	159	17
Gonorrhea	127		121	
Influenza	13	7		4
Measles	1,412	11	890	7
Pneumonia		47		85
Poliomyelitis	2		3	
Scarlet fever	243	4	157	5
Smallpox	14		40	
Syphilis	87		143	
Tuberculosis	188	108	144	101
Typhoid fever	58	8	92	7
Whooping cough	208	20	79	3

CHILE.

Mortality—Concepcion—June, 1923.

During the month of June, 1923, 221 deaths were registered at Concepcion, including 85 deaths in children under 1 year of age. Deaths from certain causes were registered as follows: Pneumonia, 55; smallpox, 2; tuberculosis, 11; typhus fever, 2.

ECUADOR.

Plague-Infected Rats—Guayaquil.

During the month of June, 1923, out of 9,000 rats examined at Guayaquil, Ecuador, 18 were found plague infected.

EGYPT.

Status of Plague.

Plague occurrence in Egypt has been reported as follows: Week ended June 24, 1923, 33 cases, of which 1 case each occurred at Alexandria and Port Said. The remaining cases were reported from nine districts, with the greatest number, viz, 12 cases, occurring in the district of Menoufieh. The total number of cases reported from January 1 to June 24, 1923, was 1,069, as compared with 263 cases reported during the corresponding period of the preceding year.

Week ended July 1, 1923, 41 cases, of which 1 case occurred at Alexandria and 2 cases at Port Said. The remaining cases were reported in eight districts, with the greatest occurrence, viz, 22 cases, in the district of Menoufieh. The total occurrence from January 1 to July 1, 1923, was 1,110 cases, as compared with 286 cases reported during the corresponding period of the preceding year.

GREAT BRITAIN.

Smallpox—Gloucestershire.[1]

On July 12, 1923, 19 new cases of smallpox were reported admitted to hospital at Gloucester, England. During the week ended July 14, 93 cases of smallpox were reported present at Gloucester.

IRAQ (MESOPOTAMIA).

Anthrax—Bagdad.

During the month of May, 1923, 2 cases of anthrax were reported at Bagdad, Iraq, of which 1 occurred in the Iraq Army and 1 was imported from outside the city.

MADAGASCAR.

Plague.

During the period June 1 to 15, 1923, 8 cases of plague with 8 deaths were reported in the island of Madagascar, occurring in the Province of Tananarive. Of these, 2 cases with 2 deaths occurred in the town of Tananarive.

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[1] Public Health Reports, July 27, 1923, p. 1739.

Rat Destruction.

During the month of May, 1923, 139,069 rats and mice were destroyed in the town of Tananarive and 44,021 rats in the neighboring district of Mandjakandriana.

PALESTINE.

Plague—Jaffa.

During the week ended June 25, 1923, 5 cases of plague with 1 death were reported at Jaffa, Palestine. Of these cases, 4 were bubonic and 1 case (with fatal termination) was septicemic.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER.

The reports contained in the following tables must not be considered as complete or final as regards either the list of countries included or the figures for the particular countries for which reports are given.

Reports Received During Week Ended August 17, 1923.[1]

CHOLERA.

Place.	Date.	Cases.	Deaths.	Remarks.
India:				
Bombay	June 10–23	23	17	
Calcutta	June 17–23	31	27	
Philippine Islands:				
Province—				
Pangasinan	June 24–30	2	2	

PLAGUE.

Ceylon:				
Colombo	June 17–23	2	2	Plague rats, 4.
China:				
Amoy	June 19–25		1	
Foochow	June 17–23			Present; endemic.
Hongkong	June 9–23	22	14	
Nanking	June 17–30			Rodent plague present.
Do	July 1–7			Do.
Ecuador:				
Guayaquil				June 1–30, 1923: Rats examined, 9,000; found infected, 18.
Egypt				Jan. 1–June 24, 1923: Cases, 1,069. Jan. 1–July 7, 1923: Cases, 1,110.
Cities—				
Alexandria	June 18–24	1		
Do	July 1–7	1		
Port Said	June 18–24	1		
Do	July 1–7	2		
India				Apr. 29–June 2, 1923: Cases, 4,240; deaths, 3,209.
Bombay	June 10–23	22	17	
Iraq (Mesopotamia):				
Bagdad	May 1–31	222	143	
Madagascar				June 1–15, 1923: Cases, 8; deaths, 8.
Province—				
Tananarive	June 1–15	8	8	Bubonic; pneumonic, septicemic.
Tananarive	do	2	2	Pneumonic; septicemic.
Palestine:				
Jaffa	June 19–25	5	1	Four bubonic; one septicemic (fatal).
Straits Settlements:				
Singapore	June 17–23	2	1	

[1] From medical officers of the Public Health Service, American consuls, and other sources.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received During Week Ended August 17, 1923—Continued.

SMALLPOX.

Place.	Date.	Cases.	Deaths.	Remarks.
Canada:				
Province—				
Ontario				July 1–31, 1923: Cases, 14.
Chile:				
Concepcion	June 5–11	1		June 1–30, 1923: Cases, 2.
Valparaiso	June 3–23	6	14	June 10–16, 1923: 29 cases reported from two districts.
China:				
Amoy	June 19–25			Present.
Foochow	June 17–23			Do.
Hongkong	June 10–23	32	22	
Nanking	June 24–July 7			Do.
Great Britain:				
Gloucester	July 12	19		July 8–14, 1923: 93 cases present.
Greece:				
Patras	May 14–June 15		8	
India:				
Bombay	June 10–23	34	19	
Calcutta	June 17–23	1	1	
Iraq (Mesopotamia):				
Bagdad	May 1–31	10		
Mexico:				
Mexico City	June 24–30	24		Including municipalities in Federal district.
Portugal:				
Oporto	July 9–15	5	4	

TYPHUS FEVER.

Bulgaria:				
Sofia	Apr. 22–May 12	8	1	Paratyphus, 1 case, 1 death.
Chile:				
Concepcion	June 12–18		1	
Valparaiso	June 4–23		13	June 11, 1923: 34 cases in the Salvador Hospital.
Greece:				
Patras	May 14–June 15		12	
Japan:				
Nagasaki	July 2–8	1		
Mexico:				
Mexico City	June 24–30	14		Including municipalities, Federal district.
Portugal:				
Oporto	July 15–21	1		

YELLOW FEVER.

Brazil:				
Bahia	June 10–16	4	1	

Reports Received from June 30 to August 10, 1923.[1]

CHOLERA.

Place.	Date.	Cases.	Deaths.	Remarks.
India				Apr. 15–June 2, 1923: Cases, 9,250; deaths, 8,126.
Bombay	June 3–9	8	3	
Calcutta	May 6–June 16	258	215	
Madras	June 3–30	2		
Rangoon	May 13–June 23	17	14	
Indo-China:				
Saigon	May 20–June 9	11	10	

[1] From medical officers of the Public Health Service, American consuls, and other sources.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

CHOLERA—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
Philippine Islands:				
City—				
Manila	June 10-16	2	1	Death in foreign case from Chingkang, China.
Province—				
Bulacan	May 17-23	1		
Capiz	May 27-June 2	1	1	
Cebu	Apr. 8-21	1	1	
Cotobato	Apr. 8-14	1	1	
Laguna	May 6-June 9	2	1	
Mountain	Mar. 25-31	1	1	
Russia (Soviet)				Jan. 1-May 15, 1923: Cases, 10.
Siam:				
Bangkok	May 13-June 9	8	9	

PLAGUE.

Australia:				
Sydney	June 30	1	1	
Azores:				
St. Michael Island	May 6-26	12	5	In one locality.
British East Africa:				
Kenya—				
Kisumu	June 10-16	2	1	
Tanganyika	May 6-June 2	3	3	Territory.
Uganda	Apr. 1-30	7	5	
Canary Islands:				
Las Palmas	June 7	1		
Ceylon:				
Colombo	May 6-June 16	13	15	Plague rats, 32.
China:				
Amoy	May 13-June 9		6	
Foochow	May 27-June 16			Present; epidemic form.
Hongkong	Apr. 29-May 26	29	14	
Manchuria—[1]				
Yakoshih	May 31	1	1	Station on Eastern Chinese Railway. Occurring in tarabagan (marmot) hunter. Bubonic.
Ecuador:				
Guayaquil				May 16-31, 1923: Rats examined, 4,800; found infected, 21.
Egypt				Jan. 1-June 21, 1923: Cases, 1,051; deaths, 548. May 1-29: Cases, 345.
City—				
Alexandria	Jan. 7-June 18	34	15	May 1-29, 1923: Cases, 14.
Port Said	Jan. 7-June 15	23	12	May 1-29, 1923: Cases, 13.
Suez	Mar. 2-June 15	12	7	May 1-29, 1923: Cases 3.
Province—				
Assiout	May 1-29	64		Deaths not reported.
Benisouef	do	7		Do.
Fayoum	do	14		Do.
Garbieh	do	2		Do.
Geizeh	do	3		Do.
Girgeh	do	123		Do.
Keneh	do	22		Do.
Menoufieh	do	34		Do.
Minieh	do	46		Do.
Hawaii:				
Hamakua				Plague-infected rats: Pohakea, May 23, 1923, 1 rat; vicinity of Pacific Sugar Co. mill, June 2, 1 rat.
India:				
Bombay	Apr. 29-June 9	479	393	
Calcutta	May 6-June 9	13	13	
Karachi	May 13-June 30	110	85	Plague rats, 5.
Madras Presidency	do	254	141	
Rangoon	May 6-June 23	226	199	

[1] Information received under date of June 27, 1923, from Dr. Wm. Lien Teh, director and chief medical officer of the North Manchuria Plague Prevention Service, states that the seven cases of plague reported as occurring at Harbin January 29-February 4, 1923 (Public Health Reports, March 23, 1923, p. 653, and subsequent issues), should have been reported as occurring in the endemic area of Transbaikal Siberia.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

PLAGUE—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
Java:				
East Java—				
Soerabaya	Apr. 1–May 19	488	488	May 1–31, 1923: Cases, 471; deaths, 471.
Soerakarta				May 16, 1923: Epidemic in five districts.
Madagascar				Apr. 1–May 15, 1923: Cases, 66; deaths, 63. Bubonic, pneumonic, septicemic.
Province—				
Tananarive	Apr. 1–May 15	48	45	
Tananarive	Apr. 16–May 15	18	18	
Mauritius Island				May 4–21, 1923: Two cases.
Port Louis	May 4	1		
Mexico:				
Tampico				Apr. 15–21, 1923: 1 plague rat.
Palestine:				
Jaffa	June 26–July 2	3		
Peru				May 1–31, 1923: Cases, 57; deaths, 27.
Locality—				
Ayabaca	May 16–31	2		
Callao	May 1–31	3	1	
Canete	May 16–31	2	2	
Cerro Azul	May 1–31	3	1	
Chiclayo	do	8	2	
Cutervo	May 1–15	2	1	
Huancabamba	May 1–31	18	13	
Lima (city)	do	5	1	
Lima (country)	do	5	3	
Salaverry	do	7	2	
Trujillo	do	2	1	
Russia				Jan. 1–May 15, 1923: Few cases in Far East regions.
Siam:				
Bangkok	Apr. 29–June 9	24	21	
Siberia				Sporadic cases of plague reported yearly in localities vicinity of stations Matsievskaya and Borzia, Transbaikal Railway.
Haranhor	May 6	1	1	Village in zone of endemic tarabagan (marmot) plague, Transbaikal Region.
Station No. 83				Station on Transbaikal Railway. Marmot plague during recent years.
Soktu				Do.
Straits Settlements:				
Singapore	May 6–June 16	4	6	
Syria:				
Beirut	May 12–21	1		

SMALLPOX.

Algeria:				
Algiers	May 1–31	2		
Arabia:				
Aden	May 27–June 2		1	
Bolivia:				
La Paz	Apr. 1–30	1	2	
Brazil:				
Pernambuco	May 6–June 16	5		
Rio de Janeiro	May 13–June 23	10	2	
British East Africa:				
Kenya—				
Mombasa	May 20–26	1		From vessel from Bombay.
Tanganyika	Apr. 29–May 5	2		
Uganda—				
Entebe	Apr. 1–30	4		
Canada:				
Alberta—				
Calgary	May 27–June 2	1		Infection from Deer Lodge, Mont.
British Columbia—				
Vancouver	May 27–June 23	31		
Manitoba—				
Winnipeg	June 3–30	4		

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER.—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

SMALLPOX—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
Canada—Continued.				
New Brunswick—				
Kent County	July 1-7	1		
Ontario				June 1-30, 1923: Cases, 13.
Toronto	June 24-30	3		
Do	July 15-21	1		
Quebec—				
Quebec	June 10-16	1		Varioloid.
Saskatchewan—				
Moose Jaw	July 8-14	1		
Regina	June 24-30	3		
Ceylon:				
Colombo	May 6-June 2	23	1	
Chile:				
Concepcion	May 22-June 11		3	
Valparaiso	May 7-June 2		107	
China:				
Amoy	May 13-June 16		3	
Antung	May 14-20	1		
Chungking	May 13-June 16			Present and endemic.
Foochow	do			Do.
Hongkong	Apr. 29-May 26	33	31	
Manchuria—				
Dairen	May 21-27	1		
Harbin	May 7-June 3	4		
Mukden	May 13-20	1		
Nanking	May 13-June 23			Do.
Shanghai	May 21-June 3	4		Foreign.
Do	July 2-8	1	2	Cases, foreign; deaths, Chinese.
Chosen (Korea):				
Chemulpo	May 1-31	1		
Fusan	do	1		
Gensan	do	1		
Seoul	do	33	9	
Cuba:				
Antilla	July 8-14		2	From Preston.
Czechoslovakia				Jan.-Mar., 1923: Cases, 15.
Ecuador:				
Guayaquil	May 16-31	1		
Egypt:				
Cairo	Mar. 12-Apr. 22	9	3	
Finland				May 1-15, 1923: 1 case.
Great Britain:				
Birmingham	June 18-30	3		
Bristol	June 28			Present.
Cardiff	June 3-30	6		
Gloucester	June 28			123 cases reported in hospital; present in rural districts.
Nottingham	June 3-9	1		
Greece				May 1-31, 1923: Cases, 211.
Athens	May 1-31	53		
Patras	Apr. 24-May 13		11	
Saloniki	Apr. 30-May 20	2	2	
India				Apr. 15-May 5, 1923: Cases, 4,973; deaths, 1,424.
Bombay	Apr. 22-May 19	246	114	
Calcutta	May 13-June 9	12	9	
Karachi	May 13-June 30	24	8	
Madras	May 13-June 23	91	16	
Rangoon	May 6-June 23	107	60	
Indo-China:				
Saigon	May 20-June 23	28	20	Including 100 surrounding square kilometers.
Iraq (Mesopotamia):				
Bagdad	Apr. 1-30	10		
Italy:				
Turin	May 28-June 3	1		
Jamaica				May 27-June 30, 1923: Cases, 226.
Kingston	May 27-June 30	39		July 1-7, 1923: Cases, 13. (Reported as alastrim.)
Do	July 1-7	12		
Japan:				
Kobe	May 28-June 10	2		
Java:				
East Java—				
Soerabaya	Apr. 22-June 2	129	19	
West Java—				
Batavia	May 5-June 8	17	3	Province.
Latvia				Apr. 1-30, 1923: Cases, 3.

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

SMALLPOX—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
Mexico:				
Aguascalientes	July 8–14		1	
Chihuahua	June 11–24	7		
Mexico City	May 19–June 23	140		Including municipalities in Federal District.
Palestine:				
Jaffa	June 5–11	1		
Persia:				
Tabriz	Apr. 1–14		1	District.
Teheran	Feb. 22–May 14		28	
Portugal:				
Lisbon	May 20–June 30	35	1	May 28–June 9, 1923: Cases, 8; deaths, 2.
Oporto	June 10–30	6	3	
Portuguese West Africa:				
Angola—				
Loanda	Apr. 1–21		2	
Rhodesia (British Africa):				
Northern Rhodesia	May 8–14	21	8	
Southern Rhodesia	May 3–16	4	2	
Siam:				
Bangkok	Apr. 29–June 9	62	33	
Sierra Leone:				
Kaballa	May 1–15	1		
Pujehun	May 16–31	1		In Sembehun district.
Spain:				
Barcelona	May 31–June 6		1	
Valencia	May 15–June 30	44	2	
Do	July 1–7	8	1	
Switzerland:				
Basel	May 27–June 30	4		
Berne	May 20–June 30	11		
Lucerne	May 1–June 7	36		
Zurich	May 20–June 23	10		
Syria:				
Damascus	May 15–June 11	7		
Tunis:				
Bizerta	June 10–20	1		
Tunis	June 11–17	1		
Do	June 26–July 1	1		
Turkey:				
Constantinople	May 13–June 26		45	
Do	June 27–July 3		4	
Union of South Africa				May 1–31, 1923: Cases, 33; deaths, 1 (colored).
Cape Province				May 1–31, 1923: Cases, 32 (colored).
Do	May 6–June 9			Outbreaks.
Orange Free State	Apr. 29–May 14			Do.
Transvaal				May 1–31, 1923: 1 case.
Do	May 26–June 9			Outbreaks.
Yugoslavia:				
Serbia—				
Belgrade	June 10–16	1	1	
On vessel:				
S. S. Kargola	May 20–26	1		At Mombasa, British East Africa; vessel arrived from Bombay Mar. 25, 1923.
S. S. Makura	May 26	2		Two cases, in quarantine (reported as alastrim). Vessel left Victoria, B. C., Apr. 28, 1923. Touched at Honolulu.

TYPHUS FEVER.

Algeria:				
Algiers	May 1–31	41	14	
Argentina:				
Rosario	May 25–31		3	
Chile:				
Concepcion	May 22–June 4		2	
Talcahuano	May 13–19	1		
Valparaiso	May 7–June 2		13	

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

TYPHUS FEVER—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
China:				
Antung	May 28–June 24	12		
Hankow	May 19–25	1		
Manchuria—				
Harbin	May 6–13	1		
Mukden	May 14–20	2		
Czechoslovakia				Jan.–Mar., 1923: Cases, 191; deaths, 6.
Egypt:				
Alexandria	May 14–June 24	7	5	
Do	June 25–July 1	2	2	
Cairo	May 12–Apr. 15	11	8	
France:				
Marseille	Mar. 1–May 31		3	
Germany:				
Coblenz	May 27–June 2		1	
Hamburg	May 20–26	3		
Königsberg	May 13–June 2	2		
Stettin	May 27–June 9	1	1	
Greece				May 1–31, 1923: Cases, 876.
Athens	May 1–31	150	5	
Patras	Apr. 24–May 13		18	
Piraeus	May 1–31	353	11	
Saloniki	Apr. 30–May 27	27	1	Recurrent typhus: Cases, 3; deaths, 3.
Guatemala:				
Guatemala City	Apr. 1–June 30		5	
Hungary				Jan. 1–May 19, 1923: Cases, 318; deaths, 36. In 11 counties.
Budapest	Jan. 1–June 2	48	12	
Irak (Mesopotamia):				
Bagdad	Apr. 1–30	2		
Latvia				Apr. 1–30, 1923: Cases, 93.
Mexico:				
Mexico City	May 20–June 23	61		Including municipalities in Federal district.
Palestine:				
Jaffa	May 22–28	2		
Do	June 26–July 9	4		Relapsing fever, 1 case.
Jerusalem	May 22–28	1		
Persia:				
Tabriz	Apr. 1–14	2		
Teheran	Feb. 22–May 14		2	
Poland				Mar. 4–Apr. 7, 1923: Cases, 2,253; deaths, 172. Recurrent typhus: Cases, 338; deaths, 6.
Portugal:				
Oporto	June 10–16	1		
Do	July 1–7	2		
Rumania:				
Kishineff	May 1–31	28		
Russia				Jan. 1–Apr. 30, 1923: Cases, 105,854. (Corresponding period 1922: Cases, 847,516.) Feb. 1–28, 1923: Cases, 17,577. Recurrent, Jan. 1–Feb. 28, 1923: Cases, 43,510.
European Russia and autonomous republics	Jan. 1–Apr. 30	93,999		
Siberia, Caucasus, and Central Asia	do	9,921		
Waterways and railways	do	2,934		
Spain:				
Barcelona	June 21–27		1	
Madrid	May 1–31		1	
Syria:				
Aleppo	May 20–June 16	4	2	
Beirut	May 1–10	1		
Tunis:				
Tunis	May 28–June 24	3	2	
Do	July 9–15	1	1	
Turkey:				
Constantinople	May 13–June 26		15	
Do	June 27–July 3		1	

CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER—Continued.

Reports Received from June 30 to August 10, 1923—Continued.

TYPHUS FEVER—Continued.

Place.	Date.	Cases.	Deaths.	Remarks.
Union of South Africa				May 1–31, 1923: Cases, 102; deaths, 21 (colored). White—Cases, 6. Total, 108 cases, 21 deaths.
Cape Province				May 1–31, 1923: Cases, 49 (colored); white, 5.
Do	Apr. 29–June 9			Outbreaks.
Natal				May 1–31, 1923: One case (colored).
Orange Free State				May 1–31, 1923: Cases, 45 (colored).
Do	May 6–26			Outbreaks.
Transvaal				May 1–31, 1923: Cases, 7.
Do	May 6–12			Outbreaks.
Johannesburg	May 1–31	1	3	
Yugoslavia:				
Croatia—				
Zagreb	May 27–June 2	1		

YELLOW FEVER.

Brazil:				
Bahia	May 13–June 9	17	5	